WEST Search History

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DATE: Monday, June 21, 2004

Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=ADJ	
☐	L8	l5 and th2 adj5 th1	145
☐	L7	L6 and th2 adj5 th1	145
☐	L6	L5 and (th2 or th1)	1152
☐	L5	cpg or immunostimulatory sequence or iss or immunostimulatory nucleic acid	41966
☐	L4	L3 and (th1 or th2)	27
☐	L3	L1 and (cpg or immunostimulatory sequence or iss or immunostimulatory nucleic acid)	45
☐	L2	krieg-arthur.in.	0
☐	L1	krieg-arthur-m.in.	47

END OF SEARCH HISTORY

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  (FILE 'HOME' ENTERED AT 13:50:11 ON 21 JUN 2004)

     FILE 'BIOSIS, MEDLINE, AGRICOLA, EMBASE, CABA, WPIDS, JAPIO, BIOTECHDS,
     LIFESCI, CAPLUS' ENTERED AT 13:50:21 ON 21 JUN 2004
                E KRIEG ARTHUR M/AU
L1            0 S E1 AND E3
L2          358 S E1 OR E3
L3          279 S L2 AND (CPG OR ISS OR IMMUNOSTIMULATORY NUCLEIC ACID)
L4           13 S L3 AND TH2 (5A) TH1
L5           10 DUP REM L4 (3 DUPLICATES REMOVED)

     FILE 'STNGUIDE' ENTERED AT 13:53:24 ON 21 JUN 2004

     FILE 'BIOSIS, MEDLINE, AGRICOLA, EMBASE, CABA, WPIDS, JAPIO, BIOTECHDS,
     LIFESCI, CAPLUS' ENTERED AT 13:56:01 ON 21 JUN 2004

     FILE 'BIOSIS, MEDLINE, AGRICOLA, EMBASE, CABA, WPIDS, JAPIO, BIOTECHDS,
     LIFESCI, CAPLUS' ENTERED AT 13:57:44 ON 21 JUN 2004
L6         42914 S CPG OR ISS OR IMMUNOSTIMULATORY NUCLEIC ACID
L7           393 S L6 AND TH2 (5A) TH1
L8           159 DUP REM L7 (234 DUPLICATES REMOVED)

=>
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Search Results - Record(s) 1 through 20 of 27 returned.

☐ 1. Document ID: US 20040106568 A1

Using default format because multiple data bases are involved.

L4: Entry 1 of 27 File: PGPB Jun 3, 2004

PGPUB-DOCUMENT-NUMBER: 20040106568
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040106568 A1

TITLE: Methods for treating and preventing infectious disease

PUBLICATION-DATE: June 3, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Krieg, Arthur M.	Wellesley	MA	US	
Klinman, Dennis	Potomac	MD	US	
Steinberg, Alfred D.	Potomac	MD	US	

US-CL-CURRENT: 514/44; 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 2. Document ID: US 20040092472 A1

L4: Entry 2 of 27 File: PGPB May 13, 2004

PGPUB-DOCUMENT-NUMBER: 20040092472
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040092472 A1

TITLE: Nucleic acid compositions for stimulating immune responses

PUBLICATION-DATE: May 13, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Krieg, Arthur M.	Wellesley	MA	US	

h e b b g e e e f e ef b e

US-CL-CURRENT: 514/44; 424/185.1, 424/186.1, 424/190.1, 424/191.1, 424/85.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

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3. Document ID: US 20040087538 A1

L4: Entry 3 of 27 File: PGPB May 6, 2004

PGPUB-DOCUMENT-NUMBER: 20040087538
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040087538 A1

TITLE: Methods of treating cancer using immunostimulatory oligonucleotides

PUBLICATION-DATE: May 6, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Krieg, Arthur M.	Wellesley	MA	US	
Weiner, George	Iowa City	IA	US	

US-CL-CURRENT: 514/44; 435/6, 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

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4. Document ID: US 20040067905 A1

L4: Entry 4 of 27 File: PGPB Apr 8, 2004

PGPUB-DOCUMENT-NUMBER: 20040067905
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040067905 A1

TITLE: Nucleic acid compositions for stimulating immune responses

PUBLICATION-DATE: April 8, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Krieg, Arthur M.	Wellesley	MA	US	

US-CL-CURRENT: 514/44; 424/185.1, 424/85.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

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5. Document ID: US 20040053880 A1

L4: Entry 5 of 27 File: PGPB Mar 18, 2004

h e b b g e e e f e ef b e

PGPUB-DOCUMENT-NUMBER: 20040053880
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040053880 A1

TITLE: Nucleic acid compositions for stimulating immune responses

PUBLICATION-DATE: March 18, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Krieg, Arthur M.	Wellesley	MA	US	

US-CL-CURRENT: 514/44; 424/186.1, 424/190.1, 424/191.1, 424/85.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 6. Document ID: US 20030224010 A1

L4: Entry 6 of 27 File: PGPB Dec 4, 2003

PGPUB-DOCUMENT-NUMBER: 20030224010
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030224010 A1

TITLE: Use of nucleic acids containing unmethylated CpG dinucleotide as an adjuvant

PUBLICATION-DATE: December 4, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Davis, Heather L.	Ottawa	MA	CA	
Schorr, Joachim	Hilden		DE	
Krieg, Arthur M.	Wellesley		US	

US-CL-CURRENT: 424/185.1; 424/204.1, 424/234.1, 514/44, 514/54

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 7. Document ID: US 20030212026 A1

L4: Entry 7 of 27 File: PGPB Nov 13, 2003

PGPUB-DOCUMENT-NUMBER: 20030212026
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030212026 A1

TITLE: Immunostimulatory nucleic acids

h e b b g e e e f e ef b e

PUBLICATION-DATE: November 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Krieg, Arthur M.	Wellesley	MA	US	
Schetter, Christian	Hilden		DE	
Vollmer, Jorg	Dusseldorf		DE	

US-CL-CURRENT: 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

---

8. Document ID: US 20030191079 A1

L4: Entry 8 of 27 File: PGPB Oct 9, 2003

PGPUB-DOCUMENT-NUMBER: 20030191079
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030191079 A1

TITLE: Methods for treating and preventing infectious disease

PUBLICATION-DATE: October 9, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Krieg, Arthur M.	Wellesley	MA	US	
Klinman, Dennis	Potomac	MD	US	
Steinberg, Alfred D.	Potomac	MD	US	

US-CL-CURRENT: 514/44; 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

---

9. Document ID: US 20030148976 A1

L4: Entry 9 of 27 File: PGPB Aug 7, 2003

PGPUB-DOCUMENT-NUMBER: 20030148976
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030148976 A1

TITLE: Combination motif immune stimulatory oligonucleotides with improved activity

PUBLICATION-DATE: August 7, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Krieg, Arthur M.	Wellesley	MA	US	

h e b b g e e e f e ef b e

Vollmer, Jorg Duesseldorf DE

US-CL-CURRENT: 514/44; 435/6, 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

---

10. Document ID: US 20030139364 A1

L4: Entry 10 of 27 File: PGPB Jul 24, 2003

PGPUB-DOCUMENT-NUMBER: 20030139364
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030139364 A1

TITLE: Methods and products for enhancing immune responses using imidazoquinoline compounds

PUBLICATION-DATE: July 24, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Krieg, Arthur M.	Wellesley	MA	US	
Schetter, Christian	Hilden	MA	DE	
Bratzler, Robert L.	Concord		US	
Vollmer, Jorg	Dusseldorf		DE	
Jurk, Marion	Dusseldorf		DE	
Bauer, Stefan	Muenchen		DE	

US-CL-CURRENT: 514/44; 435/7.1, 514/171, 514/2, 514/263.38, 514/292

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

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11. Document ID: US 20030100527 A1

L4: Entry 11 of 27 File: PGPB May 29, 2003

PGPUB-DOCUMENT-NUMBER: 20030100527
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030100527 A1

TITLE: Immunostimulatory nucleic acid molecules for activating dendritic cells

PUBLICATION-DATE: May 29, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Krieg, Arthur M.	Wellesley	MA	US	
Hartmann, Gunther	Munchen		DE	

h e b b g e e e f e ef b e

US-CL-CURRENT: 514/44; 424/93.21, 435/372, 435/455

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

12. Document ID: US 20030091599 A1

L4: Entry 12 of 27 File: PGPB May 15, 2003

PGPUB-DOCUMENT-NUMBER: 20030091599
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030091599 A1

TITLE: Use of nucleic acids containing unmethylated CpG dinucleotide as an adjuvant

PUBLICATION-DATE: May 15, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Davis, Heather L.	Ottawa	MA	CA	
Schorr, Joachim	Hilden		DE	
Krieg, Arthur M.	Wellesley		US	

US-CL-CURRENT: 424/278.1; 424/204.1, 435/6, 514/44, 514/54

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

13. Document ID: US 20030050268 A1

L4: Entry 13 of 27 File: PGPB Mar 13, 2003

PGPUB-DOCUMENT-NUMBER: 20030050268
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030050268 A1

TITLE: Immunostimulatory nucleic acid for treatment of non-allergic inflammatory diseases

PUBLICATION-DATE: March 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Krieg, Arthur M.	Wellesley	MA	US	
Berg, Daniel J.	Iowa City	IA	US	

US-CL-CURRENT: 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

h e b b g e e e f e ef b e

14. Document ID: US 20030050261 A1

L4: Entry 14 of 27 File: PGPB Mar 13, 2003

PGPUB-DOCUMENT-NUMBER: 20030050261
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030050261 A1

TITLE: Immunostimulatory nucleic acid molecules

PUBLICATION-DATE: March 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Krieg, Arthur M.	Iowa City	IA	US	
Kline, Joel	Iowa City	IA	US	
Klinman, Dennis	Potomac	MD	US	
Steinberg, Alfred D.	Potomac	MD	US	

US-CL-CURRENT: 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

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15. Document ID: US 20020164341 A1

L4: Entry 15 of 27 File: PGPB Nov 7, 2002

PGPUB-DOCUMENT-NUMBER: 20020164341
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020164341 A1

TITLE: Use of nucleic acids containing unmethylated CpG dinucleotide as an adjuvant

PUBLICATION-DATE: November 7, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Davis, Heather L.	Ottawa	MA	CA	
Schorr, Joachim	Hilden		DE	
Krieg, Arthur M.	Wellesley		US	

US-CL-CURRENT: 424/184.1; 424/278.1, 424/282.1, 424/283.1, 514/44, 514/54, 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

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16. Document ID: US 20020064515 A1

L4: Entry 16 of 27 File: PGPB May 30, 2002

h e b b g e e e f e ef b e

PGPUB-DOCUMENT-NUMBER: 20020064515
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020064515 A1

TITLE: Methods and products for stimulating the immune system using immunotherapeutic oligonucleotides and cytokines

PUBLICATION-DATE: May 30, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Krieg, Arthur M.	Iowa City	IA	US	
Weiner, George	Iowa City	IA	US	

US-CL-CURRENT: 424/85.1; 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

---

17. Document ID: US 6653292 B1

L4: Entry 17 of 27 File: USPT Nov 25, 2003

US-PAT-NO: 6653292
DOCUMENT-IDENTIFIER: US 6653292 B1

TITLE: Method of treating cancer using immunostimulatory oligonucleotides

DATE-ISSUED: November 25, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Krieg; Arthur M.	Iowa City	IA		
Weiher; George	Iowa City	IA		

US-CL-CURRENT: 514/44; 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

---

18. Document ID: US 6429199 B1

L4: Entry 18 of 27 File: USPT Aug 6, 2002

US-PAT-NO: 6429199
DOCUMENT-IDENTIFIER: US 6429199 B1

TITLE: Immunostimulatory nucleic acid molecules for activating dendritic cells

DATE-ISSUED: August 6, 2002

h e b b g e e e f e ef b e

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Krieg; Arthur M.	Iowa City	IA		
Hartmann; Gunther	Munchen			DE

US-CL-CURRENT: 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

19. Document ID: US 6406705 B1

L4: Entry 19 of 27 File: USPT Jun 18, 2002

US-PAT-NO: 6406705
DOCUMENT-IDENTIFIER: US 6406705 B1

TITLE: Use of nucleic acids containing unmethylated CpG dinucleotide as an adjuvant

DATE-ISSUED: June 18, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Davis; Heather L.	Ottawa			CA
Schorr; Joachim	Hilden			DE
Krieg; Arthur M.	Iowa City	IA		

US-CL-CURRENT: 424/278.1; 424/204.1, 424/279.1, 424/282.1, 536/23.72, 930/200, 930/210, 930/220

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

20. Document ID: US 6339068 B1

L4: Entry 20 of 27 File: USPT Jan 15, 2002

US-PAT-NO: 6339068
DOCUMENT-IDENTIFIER: US 6339068 B1
**** See image for Certificate of Correction ****

TITLE: Vectors and methods for immunization or therapeutic protocols

DATE-ISSUED: January 15, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Krieg; Arthur M.	Iowa City	IA		
Davis; Heather L.	Ottawa			CA
Wu; Tong	Hull			CA
Schorr; Joachim	Hilden			DE

h e b b g e e e f e ef b e

US-CL-CURRENT: 514/44; 424/93.2, 435/320.1, 435/455, 435/91.4, 435/91.41, 435/91.42

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Draw D

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Term	Documents
TH1	8741
TH1S	28
TH2	13539
TH2S	48
(3 AND (TH2 OR TH1)).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	27
(L3 AND (TH1 OR TH2)).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	27

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E3          336 --> KRIEG ARTHUR M/AU
E4           67     KRIEG B/AU
E5            2     KRIEG B F/AU
E6            1     KRIEG B P/AU
E7           21     KRIEG BENNO/AU
E8           11     KRIEG BERNHARD/AU
E9           41     KRIEG C/AU
E10          12     KRIEG C J/AU
E11           1     KRIEG C L/AU
E12           3     KRIEG C P/AU

=> s e1 and e3
L1            0 "KRIEG ARTHUR"/AU AND "KRIEG ARTHUR M"/AU

=> s e1 or e3
L2          358 "KRIEG ARTHUR"/AU OR "KRIEG ARTHUR M"/AU

=> s l2 and (cpg or iss or immunostimulatory nucleic acid)
L3          279 L2 AND (CPG OR ISS OR IMMUNOSTIMULATORY NUCLEIC ACID)

=> s l3 and th2 (5a) th1
L4           13 L3 AND TH2 (5A) TH1

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5           10 DUP REM L4 (3 DUPLICATES REMOVED)

=> d bib ab 1-10

L5   ANSWER 1 OF 10     MEDLINE on STN
AN   2002427392     MEDLINE
DN   PubMed ID: 12184918
TI   B cells express Ly-6C in a Th1 but not Th2 cytokine
     environment.
AU   Schlueter Annette J; Krieg Arthur M; De Vries Peter; Li Xiang
CS   Department of Pathology, University of Iowa College of Medicine, Iowa
     City, IA 52242-1181, USA.. schluetera@uihc.uiowa.edu
SO   Journal of interferon & cytokine research : official journal of the
     International Society for Interferon and Cytokine Research, (2002 Jul) 22
```

(7) 799-806.
Journal code: 9507088. ISSN: 1079-9907.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200302
ED Entered STN: 20020820
Last Updated on STN: 20030212
Entered Medline: 20030211
AB Interferon-alpha (IFN-alpha) is the primary regulator of transient Ly-6C expression on T cells. B cells, which do not express Ly-6C in the resting state, have been reported to express Ly-6C following exposure to proinflammatory stimuli. This study examined the factors controlling Ly-6C expression on B cells and the kinetics of Ly-6C expression in the presence of these factors. In vivo studies demonstrated that proinflammatory (Th1) cytokines transiently upregulate B cell Ly-6C expression. In vitro studies identified Th1 cytokines, particularly IFN-alpha and IFN-gamma, as the principal cytokines responsible for this induction. Polyclonal B cell activators (anti-IgM and recombinant CD40 ligand trimer) showed minimal ability to independently induce Ly-6C expression on B cells but did enhance the ability of IFNs to induce expression. Th2 cytokine environments did not result in B cell Ly-6C expression, and interleukin-4 (IL-4) actually antagonized the IFN-driven induction of Ly-6C. Ly6.1 strains of mice consistently demonstrated a greater ability to express Ly-6C on B cells than did Ly-6.2 strains. Together, these studies demonstrate the ability of **Th1** but not **Th2** cytokine environments to transiently induce the expression of Ly-6C on B cells and provide additional evidence for differences in the regulation of Ly-6C expression in Ly6.1 and Ly6.2 strains.

L5 ANSWER 2 OF 10 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:440338 BIOSIS
DN PREV200100440338
TI **Immunostimulatory nucleic acid** molecules.
AU **Krieg, Arthur M.** [Inventor]; Kline, Joel [Inventor, Reprint author]; Klinman, Dennis [Inventor]; Steinberg, Alfred D. [Inventor]
CS Iowa City, IA, USA
ASSIGNEE: University of Iowa Research Foundation; Coley Pharmaceutical Group, Inc., Wellesley, MA, USA; The United States of America as represented by the Department of Health and Human Services
PI US 6207646 March 27, 2001
SO Official Gazette of the United States Patent and Trademark Office Patents, (Mar. 27, 2001) Vol. 1244, No. 4. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 19 Sep 2001
Last Updated on STN: 22 Feb 2002
AB Nucleic acids containing unmethylated **CpG** dinucleotides and therapeutic utilities based on their ability to stimulate an immune response and to redirect a **Th2** response to a **Th1** response in a subject are disclosed.

L5 ANSWER 3 OF 10 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:56772 BIOSIS
DN PREV200100056772
TI **CpG** DNA is an effective oral adjuvant to protein antigens in mice.
AU McCluskie, Michael J.; Weeratna, Risini D.; **Krieg, Arthur M.**; Davis, Heather L. [Reprint author]
CS Loeb Health Research Institute, Ottawa Hospital, 725 Parkdale Avenue, Ottawa, Ont, K1Y 4E9, Canada

hdavis@lri.ca
SO Vaccine, (22 November, 2000) Vol. 19, No. 7-8, pp. 950-957. print.
CODEN: VACCDE. ISSN: 0264-410X.
DT Article
LA English
ED Entered STN: 24 Jan 2001
Last Updated on STN: 12 Feb 2002
AB We have previously reported that synthetic oligodeoxynucleotides containing immunostimulatory **CpG** motifs (**CpG** ODN) are potent adjuvants to protein administered by intramuscular (IM) injection or intranasal (IN) inhalation to BALB/c mice. Herein, we have evaluated oral delivery of **CpG** ODN with purified hepatitis B surface antigen (HBsAg) or tetanus toxoid (TT) to determine its potential as an adjuvant to oral vaccines. **CpG** ODN augmented systemic (IgG in plasma, CTL, T-cell proliferation) and mucosal (IgA in lung, vaginal or gut washes, feces and saliva) immune responses against both antigens. **CpG** stimulated both T-helper type 1 (**Th1**) (CTL, IgG2a) and **Th2** (IgG1, IgA) responses when delivered orally. Results from this study indicate that stimulatory **CpG** ODN may be effective as an adjuvant with oral vaccines.

L5 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:101856 CAPLUS
DN 130:266120
TI **CpG** oligodeoxynucleotides can circumvent the Th2 polarization of neonatal responses to vaccines but may fail to fully redirect Th2 responses established by neonatal priming
AU Kovarik, Jiri; Bozzotti, Paola; Love-Homan, Laurie; Pihlgren, Maria; Davis, Heather L.; Lambert, Paul-Henri; **Krieg, Arthur M.**; Siegrist, Claire-Anne
CS World Health Organization Collaborating Centre for Neonatal Vaccinology, University of Geneva, Geneva, 1211, Switz.
SO Journal of Immunology (1999), 162(3), 1611-1617
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB Neonatal murine responses to a panel of conventional vaccines differ qual. from adult responses by a particular polarization toward a Th2 pattern and a frequent limitation of the Th1 and CTL responses required for protection against intracellular. microorganisms. In contrast, DNA vaccines induce adult-like Th1/CTL neonatal responses against the same vaccine Ags. In this report, we show that this can be related to their content in unmethylated **CpG** motifs. Oligodeoxynucleotides (ODN) containing **CpG** motifs activate neonatal APCs to produce IL-12 in vitro and induce adult-like Th1 responses to tetanus toxoid and measles Ags in vivo, with production of IgG2a-specific Abs and adult-like secretion of IFN-γ and IL-5 by Ag-specific T cells. However, in spite of their capacity to trigger neonatal B cell proliferation in vitro, **CpG**-ODN only partially enhanced early life Ab responses. Finally, using Th1-driving **CpG**-ODN with the boosting dose of a protein vaccine was sufficient to redirect adult but not neonatally primed Th2 responses. These observations could be important for the development of novel vaccines that will have to be effective early in life.
RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:32813 CAPLUS
DN 132:346552
TI **CpG** oligodeoxynucleotides do not require TH1 cytokines to prevent eosinophilic airway inflammation in a murine model of asthma
AU Kline, Joel N.; **Krieg, Arthur M.**; Waldschmidt, Thomas J.;

Ballas, Zuhair K.; Jain, Vipul; Businga, Thomas R.
CS Departments of Medicine, University of Iowa College of Medicine, Iowa City, IA, 52242, USA
SO Journal of Allergy and Clinical Immunology (1999), 104(6), 1258-1264
CODEN: JACIBY; ISSN: 0091-6749
PB Mosby, Inc.
DT Journal
LA English
AB Oligodeoxynucleotides (ODNs) containing the dinucleotide **CpG** in a specific sequence context (**CpG**-ODNs) have the ability to prevent the development of eosinophilic airway inflammation and bronchial hyperreactivity in a murine model of asthma. The authors have previously demonstrated that **CpG**-ODNs stimulate expression of the TH1-inducing cytokines IFN-γ and IL-12 in a murine model of asthma and that this stimulation is associated with the protection against asthmatic inflammation. The purpose here was to examine whether the protection conferred by **CpG**-ODNs in a schistosome egg-egg antigen murine model of asthma is dependent on the induction of IFN-γ, IL-12, or both. C57BL/6 mice were sensitized to schistosome eggs in the presence or absence of **CpG**-ODNs or control ODNs and then stimulated with soluble egg antigen in the airway. The protection offered by **CpG**-ODNs in these mice was compared with the protection induced by **CpG**-ODNs in IL-12 and IFN-γ knockout mice and in mice treated with anticytokine blocking antibodies. Double-knockout mice (IL-12/IFN-γ) were also generated and used in these studies. Detns. included airway eosinophilic inflammation and bronchial hyperreactivity to inhaled methacholine. The authors found that **CpG**-ODNs confer protection against both airway eosinophilia and bronchial hyperreactivity in the absence of IFN-γ or IL-12 or in the presence of both cytokines together. However, in the absence of either IL-12 or IFN-γ, mice require 10 times as much **CpG**-ODNs to be protected against the induction of airway eosinophilia. The TH2 cytokines IL-4 and IL-5 were reduced in all of the **CpG**-treated mice, although less in the absence of IL-12 and IFN-γ. Thus, **CpG**-ODNs prevent the generation of TH2-like immune responses by multiple mechanisms, which involve, but do not require, IL-12 and IFN-γ. A direct suppressive effect of **CpG**-ODNs on TH2 responses is suggested by their reduction in IFN-γ and IL-12 knockout mice.
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 10 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 1
AN 1999:300763 BIOSIS
DN PREV199900300763
TI Bacterial DNA and **CpG**-containing oligodeoxynucleotides activate cutaneous dendritic cells and induce IL-12 production: Implications for the augmentation of Th1 responses.
AU Jakob, Thilo [Reprint author]; Walker, Patricia S.; **Krieg, Arthur M.**; von Stebut, Esther; Udey, Mark C.; Vogel, Jonathan C.
CS Klinik und Poliklinik fuer Dermatologie und Allergologie, Technische Universitaet Muenchen, Biedersteiner Strasse 29, D-80802, Muenchen, Germany
SO International Archives of Allergy and Immunology, (Feb.-April, 1999) Vol. 118, No. 2-4, pp. 457-461. print.
CODEN: IAAIEG. ISSN: 1018-2438.
DT Article
LA English
ED Entered STN: 12 Aug 1999
Last Updated on STN: 12 Aug 1999
AB Background: Unmethylated **CpG** sequences in bacterial DNA act as adjuvants selectively inducing Th1 predominant immune responses during genetic vaccination or when used in conjunction with protein Ag. The

precise mechanism of this adjuvant effect is unknown. Because dendritic cells (DC) are thought to be crucially involved in T cell priming and **Th1/Th2** education during vaccination via skin, we characterized the effects of bacterial DNA and **CpG**-containing oligodeoxynucleotides (**CpG** ODN) on cutaneous DC. Methods and Results: Stimulation with **CpG** ODN 1826 (6 mug/ml) induced activation of immature Langerhans cell (LC)-like DC as determined by an increased expression of MHC class II and costimulatory molecules, loss of E-cadherin-mediated adhesion and increased ability to stimulate allogeneic T cells. Composition-matched control ODN 1911 lacking **CpG** sequences at equal concentrations was without effect. In comparison to LPS and ODN 1911, **CpG** ODN 1826 selectively stimulated DC to release largeamounts of IL-12 (p40) and little IL-6 or TNF-alpha within 18 h and detectable levels of IL-12 p70 within 72 h. Stimulation with Escherichia coli DNA, but not calf thymus DNA, similarly induced DC maturation and IL-12 p40 production. Injection of **CpG** ODN into murine dermis induced enhanced expression of MHC class II and CD86 by LC in the overlying epidermis and intracytoplasmic IL-12 p40 accumulation in a subpopulation of activated LC. Conclusion: Bacterial DNA and **CpG** ODN stimulate DC in vitro and in vivo and may preferentially elicit Th1-predominant immune responses because they can activate and mobilize DC, inducing them to produce IL-12.

L5 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:436309 CAPLUS
DN 131:270519
TI Phagocytic antigen processing and effects of microbial products on antigen processing and T-cell responses
AU Ramachandra, Lakshmi; Chu, Rose S.; Askew, David; Noss, Erika H.; Canaday, David H.; Potter, N. Stevenson; Johnsen, Alyssa; **Krieg, Arthur M.** ; Nedrud, John G.; Boom, W. Henry; Harding, Clifford V.
CS Institute of Pathology, Case Western Reserve University, Cleveland, OH, 44106, USA
SO Immunological Reviews (1999), 168(Pathogen Subversion of Cellular Immunity), 217-239
CODEN: IMRED2; ISSN: 0105-2896
PB Munksgaard International Publishers Ltd.
DT Journal; General Review
LA English
AB A review with 188 refs. Processing of exogenous antigens and microbes involves contributions by multiple different endocytic and phagocytic compartments. During the processing of soluble antigens, different endocytic compartments have been demonstrated to use distinct antigen-processing mechanisms and to process distinct sets of antigenic epitopes. Processing of particulate and microbial antigens involves phagocytosis and functions contributed by phagocytic compartments. Recent data from our laboratory demonstrate that phagosomes containing antigen-conjugated latex beads are fully competent class II MHC (MHC-II) antigen-processing organelles, which generate peptide:MHC-II complexes. In addition, phagocytosed antigen enters an alternate class I MHC (MHC-I) processing pathway that results in loading of peptides derived from exogenous antigens onto MHC-I mols., in contrast to the cytosolic antigen source utilized by the conventional MHC-I antigen-processing pathway. Antigen processing and other immune response mechanisms may be activated or inhibited by microbial components to the benefit of either the host or the pathogen. For example, antigen processing and T-cell responses (e.g. **Th1** vs **Th2** differentiation) are modulated by multiple distinct microbial components, including lipopolysaccharide, cholera toxin, heat labile enterotoxin of Escherichia coli, DNA containing **CpG** motifs (found in prokaryotic and invertebrate DNA but not mammalian DNA) and components of Mycobacterium tuberculosis.
RE.CNT 188 THERE ARE 188 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:624014 CAPLUS
DN 129:259321
TI Use of nucleic acid containing unmethylated **CpG** dinucleotide as an adjuvant
IN Davis, Heather L.; Schorr, Joachim; **Krieg, Arthur M.**
PA Ottawa Civic Loeb Research Institute, Can.; Qiagen G.m.b.H.; The University of Iowa Research Foundation
SO PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9840100	A1	19980917	WO 1998-US4703	19980310
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9867595	A1	19980929	AU 1998-67595	19980310
	AU 753688	B2	20021024		
	EP 1005368	A1	20000607	EP 1998-912919	19980310
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002511841	T2	20020416	JP 1998-539730	19980310
	US 6406705	B1	20020618	US 1999-325193	19990603
	US 2002164341	A1	20021107	US 2001-23909	20011218
	US 2003091599	A1	20030515	US 2002-300247	20021120
	US 2003224010	A1	20031204	US 2003-434696	20030509
PRAI	US 1997-40376P	P	19970310		
	WO 1998-US4703	W	19980310		
	US 1998-154614	A2	19980916		
	US 1999-325193	A3	19990603		
	US 2001-23909	A1	20011218		

OS MARPAT 129:259321
AB Nucleic acids containing ≥1 unmethylated cytosine-guanine (**CpG**) dinucleotide affect immune responses by activating natural killer cells, or by redirecting the immune response from **Th2** to **Th1** to induce an immune response in a subject by inducing monocytic and other cells to produce Th1 cytokines. These nucleic acids can be used to induce an immune response by administering therapeutically effective amts. of a nucleic acid encoding an antigenic polypeptide and of an oligonucleotide containing ≥1 unmethylated **CpG** dinucleotide. This method can be applied to treating a subject having or at risk for a virus-mediated disorder such as hepatitis B. Thus, a recombinant HBsAg subunit vaccine was combined with a **CpG**-containing oligonucleotide (TCCATGACGTTCCTGACGTT with a phosphorothioate backbone) and injected i.m. into newborn or adult mice. A DNA-based vaccine was prepared from plasmid pCP10 (containing genomic hepatitis B virus sequences) and placed under the control of the cytomegalovirus promoter for direct gene transfer into mice. The response to either the protein vaccine or the DNA vaccine was enhanced by combination with the **CpG** oligonucleotide adjuvant.
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 10 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 2

AN 1999:58917 BIOSIS
DN PREV199900058917
TI **CpG** DNA can induce strong Th1 humoral and cell-mediated immune responses against hepatitis B surface antigen in young mice.
AU Millan, Cynthia L. Brazolot; Weeratna, Risini; **Krieg, Arthur M.**; Siegrist, Claire-Anne; Davis, Heather L. [Reprint author]
CS Loeb Res. Inst., 725 Parkdale Ave., Ottawa, ON K1Y 4E9, Canada
SO Proceedings of the National Academy of Sciences of the United States of America, (Dec. 22, 1998) Vol. 95, No. 26, pp. 15553-15558. print.
CODEN: PNASA6. ISSN: 0027-8424.
DT Article
LA English
ED Entered STN: 16 Feb 1999
Last Updated on STN: 16 Feb 1999
AB Successful neonatal immunization of humans has proven difficult. We have evaluated **CpG**-containing oligonucleotides as an adjuvant for immunization of young mice (1-14 days old) against hepatitis B virus surface antigen. The protein-alum-**CpG** formulation, like the DNA vaccine, produced seroconversion of the majority of mice immunized at 3 or 7 days of age, compared with 0-10% with the protein-alum or protein-**CpG** formulations. All animals, from neonates to adults, immunized with the protein-alum vaccine exhibited strong T helper (Th) 2-like responses (predominantly IgG1, weak or absent cytotoxic T lymphocytes (CTL)). Th2-type responses also were induced in young mice with protein-**CpG** (in 1-, 3-, and 7-day-old mice) and protein-alum-**CpG** (in 1- and 3-day-old mice) but immunization carried out at older ages gave mixed **Th1/Th2** (Th0) responses. DNA vaccines gave Th0-like responses when administered at 1 and 7 days of age and Th1-like (predominantly IgG2a and CTL) responses with 14-day-old or adult mice. Surprisingly, the protein-alum-**CpG** formulation was better than the DNA vaccine for percentage of seroconversion, speed of appearance, and peak titer of the antibody response, as well as prevalence and strength of CTL. These findings may have important implications for immunization of human infants.

L5 ANSWER 10 OF 10 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 3
AN 1998:33481 BIOSIS
DN PREV199800033481
TI **CpG** oligodeoxynucleotides act as adjuvants that switch on T helper 1 (Th1) immunity.
AU Chu, Rose S. [Reprint author]; Targoni, Oleg S.; **Krieg, Arthur M.**; Lehmann, Paul V.; Harding, Clifford V.
CS Inst. Pathol., Case Western Univ., Cleveland, OH 44106, USA
SO Journal of Experimental Medicine, (Nov. 17, 1997) Vol. 186, No. 10, pp. 1623-1631. print.
CODEN: JEMEAV. ISSN: 0022-1007.
DT Article
LA English
ED Entered STN: 14 Jan 1998
Last Updated on STN: 14 Jan 1998
AB Synthetic oligodeoxynucleotides (ODN) that contain unmethylated **CpG** motifs (**CpG** ODN) induce macrophages to secrete IL-12, which induces interferon (IFN)-gamma secretion by natural killer (NK) cells. Since these cytokines can induce T helper 1 (Th1) differentiation, we examined the effects of coadministered **CpG** ODN on the differentiation of Th responses to hen egg lysozyme (HEL). In both BALB/c (**Th2**-biased) and B10.D2 (**Th1**-biased) mice, immunization with HEL in incomplete Freund's adjuvant (IFA) resulted in Th2-dominated immune responses characterized by HEL-specific secretion of IL-5 but not IFN-gamma. In contrast, immunization with IFA-HEL plus **CpG** ODN switched the immune response to a Th1-dominated cytokine pattern, with high levels of HEL-specific IFN-gamma secretion and

decreased HEL-specific IL-5 production. IFA-HEL plus **CpG** ODN also induced anti-HEL IgG2a (a Th1-associated isotype), which was not induced by IFA-HEL alone. Control non-**CpG** ODN did not induce IFN-gamma or IgG2a, excepting lesser increases in B10.D2 (Th1-biased) mice. Thus, **CpG** ODN provide a signal to switch on Th1-dominated responses to coadministered antigen and are potential adjuvants for human vaccines to elicit protective Th1 immunity.

=> FIL STNGUIDE

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FULL ESTIMATED COST	0.24	52.41

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-2.77

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FULL ESTIMATED COST 11.10 63.51

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=> s cpg or iss or immunostimulatory nucleic acid
L6 42914 CPG OR ISS OR IMMUNOSTIMULATORY NUCLEIC ACID

=> s l6 and th2 (5a) th1
L7 393 L6 AND TH2 (5A) TH1

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8 159 DUP REM L7 (234 DUPLICATES REMOVED)

=> d bib ab 1-159

L8 ANSWER 1 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 1
AN 2004-257200 [24] WPIDS
DNC C2004-100451
TI New **immunostimulatory nucleic acid** molecule having pyrimidine-purine dinucleotide and a chimeric backbone, useful in treating and preventing asthma, allergy, cancer, infectious disease, autoimmune disease or airway remodeling.
DC B04 D16

IN JURK, M; KRIEG, A M; LIPFORD, G; RANKIN, R; SAMULOWITZ, U; UHLMANN, E; VOLLMER, J

PA (COLE-N) COLEY PHARM GMBH; (COLE-N) COLEY PHARM GROUP INC

CYC 104

PI WO 2004016805 A2 20040226 (200424)* EN 276
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZW

ADT WO 2004016805 A2 WO 2003-US25935 20030819

PRAI US 2003-447377P 20030214; US 2002-404479P 20020819; US 2002-404820P 20020819; US 2002-429701P 20021127

AB WO2004016805 A UPAB: 20040408

NOVELTY - An **immunostimulatory nucleic acid** molecule comprising an internal pyrimidine-purine (YZ) dinucleotide and chimeric backbone, where one internal YZ dinucleotide has a phosphodiester(-like) internucleotide linkage, where optionally each additional internal YZ dinucleotide has a phosphodiester(-like) or stabilized internucleotide linkage, where other internucleotide linkages are stabilized, is new.

DETAILED DESCRIPTION - An **immunostimulatory nucleic acid** molecule comprises at least one internal pyrimidine-purine (YZ) dinucleotide and a chimeric backbone, where at least one internal YZ dinucleotide has a phosphodiester or phosphodiester-like internucleotide linkage, where optionally each additional internal YZ dinucleotide has a phosphodiester, phosphodiester-like or stabilized internucleotide linkage and where all other internucleotide linkages are stabilized.

INDEPENDENT CLAIMS are also included for:

(1) an oligonucleotide comprising:

(a) an **immunostimulatory nucleic acid** molecule comprising a chimeric backbone and at least one sequence N1YGN2, where independently for each sequence N1YGN2, where YG is an internal pyrimidine-guanosine (YG) dinucleotide and N1 and N2 are each, independent of the other, any nucleotide and where for the at least one sequence N1YGN2 and optionally for each additional sequence N1YGN2, the YG dinucleotide has a phosphodiester or phosphodiester-like internucleotide linkage and N1 and Y and G and N2 are linked by a phosphodiester or phosphodiester-like internucleotide linkage when N1 and N2 is an internal nucleotide, respectively and where all other internucleotide linkages are stabilized; or

(b) an octameric sequence comprising at least one YZ dinucleotide having a phosphodiester or phosphodiester-like internucleotide linkage and at least 4 T nucleotides, where Y is a pyrimidine or modified pyrimidine, Z is a guanosine or modified guanosine and where the oligonucleotide includes at least one stabilized internucleotide linkage;

(2) modulating an immune response;

(3) treating airway remodeling;

(4) manufacturing a medicament of an oligonucleotide of (1) for stimulating an immune response; and

(5) stimulating an immune response.

ACTIVITY - Immunostimulant; Antiasthmatic; Antiallergic; Cytostatic; Immunosuppressive; Respiratory-Gen.; Antimicrobial; Virucide; Antibacterial; Antiparasitic.

Three groups of BALB/c mice were injected intraperitoneally with murine renal adenocarcinoma of spontaneous origin (Renca) cells. Each group received either 100 mg semi-soft oligonucleotide SEQ ID NO: 242 or an equivalent volume of phosphate buffer saline (PBS). Mice were followed for survival and tumor size death. Mice which received treatment with PBS had 20 % survival at 50 days and had tumor volumes of 1200 mm3. In contrast, in mice which received semi-soft oligonucleotide treatment had

80 % survival at 50 days and had tumor volumes of 250 mm3.

MECHANISM OF ACTION - Gene Therapy; Vaccine. No biological data given.

USE - The oligonucleotide is useful in stimulating or modulating an immune response. The medicament shifts the immune response to a **Th1** biased response from a **Th2** biased response. The oligonucleotide is also useful in the manufacture of a medicament for treating asthma, allergy, cancer, infectious disease, autoimmune disease, airway remodeling or chronic obstructive pulmonary disease or in treating a subject who is a smoker or who is free of symptoms of asthma. The oligonucleotide is useful in inducing cytokine expression, e.g. IL-6 (interleukin-6), TNF alpha (tumor necrosis factor alpha), IFN alpha (interferon-alpha), IFN gamma (interferon-gamma) and IP-10 (Interferon Inducible Protein) (all claimed). The oligonucleotide is also useful in treating and preventing infections caused by viruses, bacteria and parasites.

Dwg.0/43

L8 ANSWER 2 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:203605 CAPLUS
DN 140:216184
TI Diagnosis and treatment of infertility
IN Kwak, Kim Joanne Young Hee; Beer, Alan E.; Gilman-Sachs, Alice
PA Finch University of Health Sciences, USA
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004019764	A2	20040311	WO 2003-US27204	20030829
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004105858	A1	20040603	US 2003-651690	20030828
PRAI	US 2002-406804P	P	20020829		
	US 2003-651690	A	20030828		

AB The authors disclose regulation of immune responses for diagnosis and treatment of infertility. More particularly, methods that down-regulate T helper 1 (Th1) immunity or up-regulate T helper 2 (Th2) immunity are used to enhance reproductive outcomes in subjects with recurrent spontaneous abortions or implantation failures by changing the balance of T helper 1 and T helper 2 immune responses. Ratios of **Th1** and **Th2** activities can also be used for diagnosis of infertility in these subjects. In one example, immune deviation is achieved by administration of the tumor necrosis factor antagonist, infliximab.

L8 ANSWER 3 OF 159 MEDLINE on STN DUPLICATE 2
AN 2004215907 IN-PROCESS
DN PubMed ID: 15114682
TI **CpG** DNA redirects class-switching towards "Th1-like" Ig isotype production via TLR9 and MyD88.
AU Lin Ling; Gerth Andrea J; Peng Stanford L
CS Department of Internal Medicine/Rheumatology, Washington University School

of Medicine, St. Louis, MO 63110, USA.
NC AI01803 (NIAID)
AI057471 (NIAID)
SO European journal of immunology, (2004 May) 34 (5) 1483-7.
Journal code: 1273201. ISSN: 0014-2980.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20040429
Last Updated on STN: 20040611
AB Unmethylated **CpG**-containing DNA plays a critical role in immunity via the augmentation of **Th1** but suppression of **Th2** T cell responses. We describe here that **CpG** motifs also redirect isotype production by murine B cells to "Th1-like" Ig isotypes (IgG2a, IgG2b, and IgG3) while suppressing Th2 isotypes (IgG1 and IgE). Using genetically mutant B cells, we find that the IgG2a, IgG2b and IgG3 isotypes are transcriptionally regulated via the promotion of class-switching, in a manner critically dependent upon TLR9 and MyD88. Thus, **CpG** DNA redirects Ig isotype production by regulating the specificity of class-switch recombination.

L8 ANSWER 4 OF 159 MEDLINE on STN DUPLICATE 3
AN 2004251430 IN-PROCESS
DN PubMed ID: 14985787
TI IL-18 gene therapy develops Th1-type immune responses in Leishmania major-infected BALB/c mice: is the effect mediated by the **CpG** signaling TLR9?.
AU Li Y; Ishii K; Hisaeda H; Hamano S; Zhang M; Nakanishi K; Yoshimoto T; Hemmi H; Takeda K; Akira S; Iwakura Y; Himeno K
CS Department of Microbiology and Immunology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.
SO Gene therapy, (2004 Jun) 11 (11) 941-8.
Journal code: 9421525. ISSN: 0969-7128.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20040520
Last Updated on STN: 20040528
AB IL-18 regulates either **Th1** or **Th2** responses depending on the cytokine microenvironment. Administration of recombinant IL-18 (rIL-18) alone does not promote **Th1** response, but rather induces **Th2** response and exacerbates Leishmania major infection in susceptible BALB/c mice. Here, we treated BALB/c mice with an IL-18-expressing plasmid by using a gene gun weekly after L. major infection. This gene therapy resulted in improved pathogenic process and preferential induction of Th1 responses by inducing the expression of IL-12 p40, but treatment with rIL-18 did not. Notably, simultaneous administration of rIL-18 with an empty plasmid vector rendered BALB/c mice resistant to the infection, despite the fact that treatment with either rIL-18 alone or the plasmid vector alone did not influence the susceptibility. The synergistic role of the vector with rIL-18 was found to depend on **CpG** motifs, which enhanced expression of proinflammatory cytokines, especially IL-12, from APCs through Toll-like receptor (TLR) 9 ligation. Treatment with methylated plasmid vector in which **CpG** was disrupted could no longer prevent the disease development in coadministration with rIL-18. Taken together, IL-18 gene therapy was shown to develop Th1-type protective immunity in L. major-infected BALB/c mice without the requirement of exogenous IL-12, probably via **CpG**-TLR9 signaling pathway.

L8 ANSWER 5 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

DUPLICATE 4
AN 2004:179987 BIOSIS
DN PREV200400172347
TI Airway peptidoglycan and immunostimulatory DNA exposures have divergent effects on the development of airway allergen hypersensitivities.
AU Chisholm, Dugald; Libet, Lev; Hayashi, Tomoko; Horner, Anthony A. [Reprint Author]
CS University of California, San Diego, 9500 Gilman Dr, La Jolla, CA, 92093-0663, USA
SO Journal of Allergy and Clinical Immunology, (March 2004) Vol. 113, No. 3, pp. 448-454. print.
CODEN: JACIBY. ISSN: 0091-6749.
DT Article
LA English
ED Entered STN: 31 Mar 2004
Last Updated on STN: 31 Mar 2004
AB Background: Environmental exposures to toll-like receptor (TLR) ligands have been suggested to provide immunologic protection against allergic diseases. However, some TLRs use unique intracellular signaling pathways, suggesting that ambient TLR ligand exposures might induce a range of host responses. Objective: These investigations compared peptidoglycan (PGN; TLR2)-induced and immunostimulatory sequence DNA oligodeoxynucleotide (**ISS**-ODN; TLR9)-induced innate responses and determined how airway exposures to these TLR ligands affect adaptive immunity and the asthmatic phenotype. Methods: In in vitro and in vivo studies innate responses to PGN and **ISS**-ODN were compared. Alternatively, mice were intranasally immunized with ovalbumin (OVA) alone or OVA plus PGN or **ISS**-ODN, and adaptive immune profiles and responses to airway OVA challenge were assessed. Results: PGN and **ISS**-ODN induced divergent innate responses predictive of their having **TH2**- and **TH1**-biasing adjuvant potential, respectively. Consistent with these findings, mice intranasally immunized with OVA alone had relatively weak adaptive responses, whereas intranasal OVA/PGN- and OVA/**ISS** -ODN-coimmunized mice had much stronger humoral and cellular responses that were **TH2** and **TH1** biased, respectively. Finally, on airway allergen challenge, mice intranasally immunized with OVA alone had modest TH2-biased airway hypersensitivity responses, whereas airway responses were greatly exaggerated for intranasal OVA/PGN-immunized mice. In contrast, intranasal OVA/**ISS**-ODN-immunized mice had little evidence of airway hypersensitivity after airway allergen challenge. Conclusions: Considered in a larger context, these results suggest that inspired air is likely to contain TLR ligands capable of both preventing and precipitating the asthmatic phenotype.

L8 ANSWER 6 OF 159 MEDLINE on STN
AN 2004246630 IN-PROCESS
DN PubMed ID: 15146108
TI Toll-like receptors and immune response in allergic disease.
AU Gangloff Sophie C; Guenounou Moncef
CS Department of Immunology and Microbiology, University of Reims Champagne-Ardenne, Reims, France.
SO Clinical reviews in allergy & immunology, (2004 Apr) 26 (2) 115-26.
Journal code: 9504368. ISSN: 1080-0549.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20040518
Last Updated on STN: 20040518
AB Allergic reactions are dominated by the preferential development of specific Th2 responses against innocuous antigens in atopic individuals. This can reflect alterations in innate immune mechanisms. Toll-like receptors (TLRs) have evolved as key molecules in innate and adaptive

immunity. Their activation by structurally distinct exogenous or endogenous ligands present at the cell microenvironment plays a critical role in antimicrobial defense. The global view is that TLR activation induces antigen-presenting cells to produce cytokines that favor Th1-type immune responses, suggesting that it might prevent the development of deleterious Th2 responses in allergy. On the basis of epidemiological studies and recent data, it has been established that TLRs play a role in the development of Th2 responses. However, more information is needed to fully understand the mechanism of TLR involvement and the implication of immune cells that express TLRs in the **Th1/Th2** cytokine profiles. Several TLRs, such as TLR9, TLR7, and TLR8, can be considered as good target candidates. Some TLR ligands, such as **CpG** DNA, are effective adjuvants, strong inducers of both IL-5 and eosinophilia downregulation. They are also potential links to allergen epitopes that could provide new allergen-specific immunotherapy regimens for the treatment of allergic disorders.

L8 ANSWER 7 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 5
AN 2004:152276 BIOSIS
DN PREV200400155311
TI DNA, the immune system, and atopic disease.
AU Hussain, Iftikhar; Kline, Joel N. [Reprint Author]
CS 200 Hawkins Drive, C33GH UIHC, Iowa City, IA, 52242, USA
joel-kline@uiowa.edu
SO Journal of Investigative Dermatology Symposium Proceedings, (January 2004) Vol. 9, No. 1, pp. 23-28. print.
ISSN: 1087-0024 (ISSN print).
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 17 Mar 2004
Last Updated on STN: 17 Mar 2004
AB The prevalence and severity of atopic diseases (atopic dermatitis, asthma, and allergic rhinitis) have increased over recent decades, particularly in industrialized nations. Atopic dermatitis, like asthma, is more common in older siblings and in less crowded houses and with late entry to day care, increased maternal education, and higher socio-economic status. The inverse relationship between the incidence of atopy and childhood infections has led to the "hygiene hypothesis," which suggests that diminished exposure to childhood infections in modern society has led to decreased TH1-type responses. Reduced **TH1** may lead to enhanced **TH2**-type inflammation, which is important in promoting asthma and allergic disease. Corticosteroids, commonly used to treat these conditions, inhibit the function of inflammatory cells, but they are ineffective in altering the initial TH2-type response to allergens in a sensitized individual. Treatment with TH1 cytokines not only has failed to make any significant impact on the outcome of these diseases, but it also has caused significant adverse reactions. A novel therapeutic approach, recently reported in the preclinical setting, is the use of oligodeoxynucleotides, which contain unmethylated motifs centered on CG dinucleotides. These **CpG** oligodeoxynucleotides potently induce **TH1** cytokines and suppress **TH2** cytokines, and can prevent manifestations of asthma and other allergic diseases in animal models. They have the potential to reverse TH2-type responses to allergens and thus restore balance to the immune system without the adverse effects of TH1 cytokines.

L8 ANSWER 8 OF 159 MEDLINE on STN DUPLICATE 6
AN 2004168020 MEDLINE
DN PubMed ID: 15061114
TI [Bacteria and their role in allergic diseases].
Bakterie a jejich vztah k alergickym onemocnenim.

AU Humlova Z
CS Ustav imunologie a mikrobiologie 1. LF UK a VFN, Praha.. zhuml@lf1.cuni.cz
SO Casopis lekaru ceskych, (2004) 143 (1) 21-5. Ref: 30
Journal code: 0004743. ISSN: 0008-7335.
CY Czech Republic
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Czech
FS Priority Journals
EM 200404
ED Entered STN: 20040406
Last Updated on STN: 20040421
Entered Medline: 20040420
AB From the beginning of life, human immune system is affected by interactions with different microorganisms. Immediately after the birth bacteria colonize mucous tissues and namely the gastrointestinal tract, which was antenatally sterile. Bacteria are involved in allergic inflammation by two different ways. They can either initiate the allergic response or they can diminish it. To the negative factors, which can trigger the allergic response belong superantigens, namely the bacterial enterotoxins. Positive factors include mycobacterial antigens, intestinal microflora, pathogen-associated molecular patterns and **CpG** motives that belong to components of the bacterial genome DNA. The effect of lipopolysaccharide from gram-negative bacteria on the development of allergic inflammation is two faced. Lipopolysaccharide has a protective role when the infection precedes the contact with allergen for a long time. Short period between the infection and allergen exposition leads in a sensitized person to the provocation of allergic disease. These and other factors are important in relation to the so-called hygiene hypothesis where the T regulatory lymphocytes seem to play the key role in the balance between **Th1** and **Th2** lymphocytes.

L8 ANSWER 9 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 7
AN 2004:188929 BIOSIS
DN PREV200400191714
TI Suramin has adjuvant properties and promotes expansion of antigen-specific **Th1** and **Th2** cells in vivo.
AU Denkinger, Michael; Shive, Carey L.; Pantenburg, Birte; Forsthuber, Thomas G. [Reprint Author]
CS School of Medicine, Institute of Pathology, Case Western Reserve University, 2109 Adelbert Road, Cleveland, OH, 44106, USA
tgf2@pop.cwru.edu
SO International Immunopharmacology, (January 2004) Vol. 4, No. 1, pp. 15-24. print.
ISSN: 1567-5769 (ISSN print).
DT Article
LA English
ED Entered STN: 7 Apr 2004
Last Updated on STN: 7 Apr 2004
AB Aluminum hydroxide and incomplete Freund's adjuvant (IFA) are the only adjuvants approved for human use. Both are T helper 2 (**Th2**) adjuvants, however, T helper 1 (**Th1**) immunity is induced if microbial products such as mycobacteria, **CpG**'s, or bacterial toxins are included in the adjuvant preparation. The usefulness of bacterial toxins, such as Pertussis toxin (PT) or Cholera toxin (CT), as adjuvants for human vaccination is limited by toxic side effects and high immunogenicity. Hence, we asked whether or not the adjuvant activity of bacterial toxins on **Th1** and **Th2** immunity could be mimicked by chemical compounds of small molecular weight and less immunogenicity. In the present study, we show that Suramin, a small molecular weight naphthylurea, which mainly acts on G-proteins and on

P2X/P2Y receptors, promotes expansion of hen eggwhite lysozyme (HEL)-specific **Th1** and **Th2** cells upon immunization of BALB/c mice with HEL in aluminum hydroxide (alum). The results indicated that the adjuvant effects of Suramin on T cell responses were mediated by enhancing the expression of MHC class II and costimulatory molecules on antigen presenting cells (APCs), and by increasing their pro-inflammatory cytokine production. Together, the results suggest that small molecular weight compounds such as Suramin could be used as alternative vaccine adjuvants.

L8 ANSWER 10 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2004:288825 BIOSIS
DN PREV200400287582
TI Lentiviral Mediated Transduction of Dendritic Cell Progenitors Does Not Alter the Maturation and Antigen Presentation Function of Dendritic Cells.
AU He, Yukai [Reprint Author]; Zhang, Jiying; Mi, Zhibao; Robbins, Paul D; Falo, Louis D
CS Department of Dermatology, University of Pittsburgh, 190 Lothrop St Suite 145, Pittsburgh, PA, 15213, USA
ykhe@pitt.edu
SO FASEB Journal, (2004) Vol. 18, No. 4-5, pp. Abst. 85.16.
http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. Washington, District of Columbia, USA. April 17-21, 2004. FASEB.
ISSN: 0892-6638 (ISSN print).
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 16 Jun 2004
Last Updated on STN: 16 Jun 2004
AB Gene transfer into DCs without skewing their intrinsic function remains a critical challenge for the design of immunotherapies of infection, neoplasms, and autoimmune diseases. We investigated the effect of lentiviral vector on the phenotype and function of murine bone marrow derived DCs. We found that although maturing DCs could be transduced using lentiviral vectors, targeting DC progenitors or immature DCs resulted in improved transduction efficiency, reproducibly enabling 50% transduction of resulting DC populations. Transduction of early immature DCs or DC progenitors with lentiviral vectors did not affect the maturation or antigen presentation function of transduced DCs. Transduced and non-transduced DCs responded similarly to proinflammatory stimuli, as secretion of significant amounts of IL-12p70 could be induced by **CpG** oligonucleotides or LPS. Transduction did not affect the capacity of DCs to stimulate T cells as measured by allogenic T cell proliferation and had no effect on **Th1/Th2** skewing of T-cell responses. Transduced DCs efficiently processed and presented both MHC class I and II restricted epitopes from expressed transgenic antigens. Animals vaccinated with transduced DCs developed CTL activity and were completely protected from tumor cell challenge. These results suggest that lentiviral vectors can effectively introduce antigen-encoding genes into DCs without interfering with their antigen presentation function or **Th1/Th2** T-cell skewing capability.

L8 ANSWER 11 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:335149 CAPLUS
DN 138:352764
TI Antibodies, fragments, oligonucleotides and peptidomimetics for activating or inhibiting toll-like receptor 9 and for treating allergic and infectious diseases
IN An, Ling-Ling; Wu, Herren; Fung, Michael S. C.
PA Tanox, Inc., USA
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2

DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003035695	A2	20030501	WO 2002-US23645	20020725
	WO 2003035695	A3	20031113		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	EP 1412390	A2	20040428	EP 2002-795487	20020725

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

PRAI	US 2001-308068P	P	20010726
	WO 2002-US23645	W	20020725

AB The present invention includes mols. that bind to a peptidic segment on TLR9 and mimic the effects of the **CpG** motif. The **CpG** mimicking agents include, but are not limited to, antibodies, small-mol. compds., peptides, peptide mimetics, and nucleic acids, including compns. comprising mols. that bind to a peptidic segment on TLR9 and mimic the effects of the **CpG** motif suitable for administering to a patient in need of treatment, optionally in combination with, for example, an excipient, diluent, or carrier. In addition, the present invention includes those mols. which bind to the TLR9's CXXC motifs at 255Cys-Arg-Arg 258Cys (as CRRC) or at 265Cys-Met-GIu 268Cys (as CMEC). The present invention includes methods for modulating the immune response by inducing a Th1-type response comprising administering mols. that bind to TLR9 and mimic **CpG** function. These mols. also shift the host cellular response away from a **Th2**-type response toward the **Th1**-type response. Thus, administering the mols. of the present invention that bind to TLR9 may avoid the risk of Th2-mediated, immunization-induced anaphylaxis, making this method useful in immunotherapy and asthma treatment. The mols. of the present invention may be administered in combination with a particular allergen.

L8 ANSWER 12 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:319450 CAPLUS
DN 138:331689
TI Polarization of the helper T-cell response with **immunostimulatory nucleic acid**
IN Raz, Eyal; Broide, David
PA USA
SO U.S. Pat. Appl. Publ., 56 pp., Cont.-in-part of U.S. Ser. No. 235,742.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 12

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003078223	A1	20030424	US 2002-99512	20020315
	US 6498148	B1	20021224	US 1999-235742	19990121
	AU 759590	B2	20030417	AU 2001-23162	20010221
	US 2003203861	A1	20031030	US 2001-947209	20010904
	US 2003109469	A1	20030612	US 2002-99379	20020614
	US 2003092663	A1	20030515	US 2002-229208	20020826

PRAI US 1996-593554 B1 19960130
US 1997-927120 B2 19970905
US 1999-235742 A2 19990121
US 1999-265191 A2 19990310
US 2001-276865P P 20010316
US 1993-112440 B2 19930826
US 1995-446691 B2 19950607
AU 1997-18418 A3 19970128

AB The authors disclose methods of maintaining suppression of a **Th2** immune response and increasing a **Th1** immune response in an individual. The methods generally involve administering to an individual an effective amount of an **immunostimulatory nucleic acid**. In one example, administration of an immunostimulatory oligonucleotide suppresses pulmonary eosinophil accumulation in a Th2-driven model of asthma. Amelioration of the immunol. markers associated with asthma pathol. was shown to coincide with polarization to a type 1 helper T-cell response.

L8 ANSWER 13 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:824514 CAPLUS
DN 140:53022
TI An Immunomodulatory GpG Oligonucleotide for the Treatment of Autoimmunity via the Innate and Adaptive Immune Systems
AU Ho, Peggy P.; Fontoura, Paulo; Ruiz, Pedro J.; Steinman, Lawrence; Garren, Hideki
CS Beckman Center for Molecular Medicine, Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA, 94305, USA
SO Journal of Immunology (2003), 171(9), 4920-4926
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB Bacterial DNA and immunostimulatory **CpG** oligodeoxynucleotides (ODNs) activate the innate immune system to produce proinflammatory cytokines. Shown to be potent Th1-like adjuvants, stimulatory **CpG** motifs are currently used as effective therapeutic vaccines for various animal models of infectious diseases, tumors, allergies, and autoimmune diseases. In this study, we show that the application of an immunomodulatory GpG ODN, with a single base switch from **CpG** to GpG, can effectively inhibit the activation of Th1 T cells associated with autoimmune disease. Moreover, this immunomodulatory GpG ODN suppresses the severity of exptl. autoimmune encephalomyelitis in mice, a prototypic Th1-mediated animal disease model for multiple sclerosis.
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 14 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 8
AN 2003:308666 BIOSIS
DN PREV200300308666
TI Divergent synthetic nucleotide motif recognition pattern: Design and development of potent immunomodulatory oligodeoxyribonucleotide agents with distinct cytokine induction profiles.
AU Kandimalla, Ekambar R.; Bhagat, Lakshmi; Wang, Daqing; Yu, Dong; Zhu, Fu-Gang; Tang, Jimmy; Wang, Hui; Huang, Ping; Zhang, Ruiwen; Agrawal, Sudhir [Reprint Author]
CS Hybridon, Inc., 345 Vassar Street, Cambridge, MA, 02139, USA
sagrawal@hybridon.com
SO Nucleic Acids Research, (May 1 2003) Vol. 31, No. 9, pp. 2393-2400. print.
ISSN: 0305-1048 (ISSN print).
DT Article
LA English

ED Entered STN: 2 Jul 2003
Last Updated on STN: 2 Jul 2003

AB Unmethylated **CpG** dinucleotides present within certain specific sequence contexts in bacterial and synthetic DNA stimulate innate immune responses and induce cytokine secretion. Recently, we showed that **CpG** DNAs containing two 5'-ends, immunomers, are more potent in both regards. In this study, we show that an immunomer containing a synthetic CpR motif (R=2'-deoxy-7-deazaguanosine) is a potent immunostimulatory agent. However, the profile of cytokine induction is different from that with immunomers containing a natural **CpG** motif. In general, a CpR immunomer induced higher interleukin (IL)-12 and lower IL-6 secretion. Compared with conventional **CpG** DNAs, both types of immunomers showed a rapid and enhanced activation of the transcription factor NF-kappaB in J774 cells. NF-kappaB activation by **CpG** DNA corresponded to degradation of IkappaBalpha in J774 cells. All three immunostimulatory oligonucleotides activated the p38 mitogen-activated protein kinase pathway as expected. Immunomers containing **CpG** and CpR motifs showed potent reversal of the antigen-induced **Th2** immune response towards a **Th1** type in antigen-sensitized mouse spleen cell cultures. Immunomers containing a CpR motif showed significant antitumor activity in nude mice bearing MCF-7 human breast cancer and U87MG glioblastoma xenografts. These studies suggest the ability for a divergent synthetic nucleotide motif recognition pattern of the receptor involved in the immunostimulatory pathway and the possibility of using synthetic nucleotides to elicit different cytokine response patterns.

L8 ANSWER 15 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 9

AN 2004:208094 BIOSIS

DN PREV200400208677

TI Polarisation of a T-helper cell immune response by activation of dendritic cells with **CpG**-containing oligonucleotides: A potential therapeutic regime for bladder cancer immunotherapy.

AU Atkins, H.; Davies, B. R.; Kirby, J. A. [Reprint Author]; Kelly, J. D.

CS School of Surgical and Reproductive Sciences, Faculty of Medical Sciences, Northern Institute for Cancer Research, University of Newcastle, Framlington Place, Newcastle-Upon-Tyne, NE2 4HH, UK
j.a.kirby@ncl.ac.uk

SO British Journal of Cancer, (15 December 2003) Vol. 89, No. 12, pp. 2312-2319. print.
ISSN: 0007-0920 (ISSN print).

DT Article

LA English

ED Entered STN: 14 Apr 2004
Last Updated on STN: 14 Apr 2004

AB Intravesical bacillus Calmette-Guerin (BCG) is a treatment for transitional cell carcinoma (TCC) and carcinoma in situ (cis) of the urinary bladder, but some patients remain refractory. The mechanism of cancer clearance is not known, but T cells are thought to play a contributory role. Tissue dendritic cells (DCs) are known to initiate antigen-specific immune responses following activation of receptors, which recognise molecular patterns on the surface of microorganisms. A family of these receptors, the toll-like receptors (TLRs), are also crucial for activating DC to produce cytokines that polarise the T-cell response towards a T helper (Th)1 or Th2 phenotype. This study compared the potential of intact BCG to activate DC with that of the defined TLR4 ligand lipopolysaccharide (LPS) and the TLR9 ligand **CpG** -oligonucleotide. It was found that all three stimuli efficiently activated normal DC, but cells expressing a mutant TLR4 responded poorly to stimulation with LPS. Importantly, stimulation with BCG induced both IL-12 and IL-10, suggesting subsequent development of a poorly focused T-cell immune response containing both **Th1** and **Th2**

immune function. By contrast, LPS-and **CpG**-oligonucleotides induced only IL-12, indicating the potential to produce a Th1 response, which is likely to clear cancer most efficiently. Given the toxicity of LPS, our data suggest that **CpG**-oligonucleotides may be beneficial for intravesical therapy of bladder cancer.

L8 ANSWER 16 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 10
AN 2003:163457 BIOSIS
DN PREV200300163457
TI Cutting edge: Histamine inhibits IFN-alpha release from plasmacytoid dendritic cells.
AU Mazzoni, Alessandra; Leifer, Cynthia A.; Mullen, Gregory E. D.; Kennedy, Margaret N.; Klinman, Dennis M.; Segal, David M. [Reprint Author]
CS National Institutes of Health, Building 10, Room 4B36, Bethesda, MD, 20892-1360, USA
dave_segal@nih.gov
SO Journal of Immunology, (March 1 2003) Vol. 170, No. 5, pp. 2269-2273. print.
ISSN: 0022-1767 (ISSN print).
DT Article
LA English
ED Entered STN: 26 Mar 2003
Last Updated on STN: 26 Mar 2003
AB Plasmacytoid dendritic cells (DC) are professional APC and a major source of type I IFN following viral infection. We previously showed that histamine alters the cytokine profiles of maturing monocyte-derived DC resulting in a change from **Th1** to **Th2** in their T cell polarizing function. In this study, we show that human plasmacytoid DC, activated by either **CpG** oligodeoxynucleotides or viral infection, also respond to histamine through H2 receptors, leading to a marked down-regulation of IFN-alpha and TNF-alpha and a moderate switch in their capacity to polarize naive T cells. Our findings provide an explanation for low levels of type I IFN frequently observed in atopic individuals.

L8 ANSWER 17 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:721330 CAPLUS
DN 140:144119
TI Activation of dendritic cells using adjuvant and allergic disease therapy
AU Sano, Kunio
CS School of Medicine, Affiliated Hospital, Tohoku University, Japan
SO Gendai Iryo (2003), 35(8), 1853-1859
CODEN: GEIRDK; ISSN: 0533-7259
PB Gendai Iryosha
DT Journal; General Review
LA Japanese
AB A review. The topics discussed are (1) **Th1** and **Th2** cells in allergy; (2) conditioning of dendritic cells in Th activation; (3) immunostimulatory adjuvants; (4) **CpG** DNA motifs and Toll-like receptors (TLRs); (5) **CpG** DNA induced dendritic cell (DC) activation and Th1 cell generation; (6) enhanced **CpG** DNA-conjugated antigen uptakes by DCs; (7) Th1 cell induction by **CpG** DNA-conjugated antigens; and (8) anti-allergen effect of **CpG** DNA-conjugated antigens.

L8 ANSWER 18 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 11
AN 2003:343387 BIOSIS
DN PREV200300343387
TI An immunostimulatory oligodeoxynucleotide containing a cytidine-guanosine motif protects senescence-accelerated mice from lethal influenza virus by augmenting the T helper type 1 response.

AU Dong, Li; Mori, Isamu; Hossain, Md. Jaber; Liu, Beixing; Kimura, Yoshinobu [Reprint Author]
CS Department of Microbiology, Fukui Medical University School of Medicine, Shimoaizuki 23-3, Matsuoka-cho, Yoshida-gun, Fukui, 910-1193, Japan ykimura@fmsrsa.fukui-med.ac.jp
SO Journal of General Virology, (June 2003) Vol. 84, No. 6, pp. 1623-1628. print.
ISSN: 0022-1317 (ISSN print).
DT Article
LA English
ED Entered STN: 23 Jul 2003
Last Updated on STN: 23 Jul 2003
AB The SAM-P1 strain of senescence-accelerated model mice shows an impaired T helper type 1 (Th1) immune response upon infection with influenza virus, which results in high susceptibility to the virus. Treatment of spleen cells from SAM-P1 mice with an immunostimulatory oligodeoxynucleotide containing a cytidine-guanosine motif (**CpG** ODN) in vitro increased the ratio of the titre of IFN-gamma to that of IL-4. Administration of **CpG** ODN to SAM-P1 mice generated satisfactory virus-specific cytotoxic T-lymphocyte responses and natural killer cell activation and the virus-specific immunoglobulin (Ig) isotype switched from IgG1 to IgG2a. Virus growth in the lungs of **CpG** ODN-treated SAM-P1 mice was cleared quickly and mice survived the lethal influenza virus infection. It could be inferred that a possible mechanism of **CpG** ODN for normalization of senescence-associated dysregulation of the **Th1/Th2** balance involves the upregulated expression of CD154 and CD40 molecules on immune-competent cells. These results suggest that **CpG** ODN could contribute to the development of a protective strategy against infectious diseases, especially among immunocompromised elderly persons, by stimulating Th1 immune responses.

L8 ANSWER 19 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 12
AN 2003:314504 BIOSIS
DN PREV200300314504
TI Targeting of immunostimulatory DNA cures experimental visceral leishmaniasis through nitric oxide up-regulation and T cell activation.
AU Datta, Neeta; Mukherjee, Snigdha; Das, Lopamudra; Das, Pijush K. [Reprint Author]
CS Molecular Cell Biology Laboratory, Indian Institute of Chemical Biology, 4 Raja S. C. Mullick Road, Calcutta, 700032, India pijushkdas@vsnl.com
SO European Journal of Immunology, (June 2003) Vol. 33, No. 6, pp. 1508-1518. print.
ISSN: 0014-2980 (ISSN print).
DT Article
LA English
ED Entered STN: 9 Jul 2003
Last Updated on STN: 22 Aug 2003
AB Active targeting of **CpG**-containing oligodeoxynucleotide (**CpG**-ODN) to macrophages was studied by incorporating it in mannose-coated liposomes, using visceral leishmaniasis as the model macrophage disease. Mannosylated liposomal **CpG**-ODN was more effective than liposomal or free **CpG**-ODN in inhibiting amastigote multiplication within macrophages. Moreover, in a 60-day mouse model of visceral leishmaniasis, complete elimination of spleen parasite burden was achieved by mannosylated liposomal **CpG**-ODN, compared to 62% and 81% parasite suppression by free and liposomal ODN, respectively, at a similar dose. Although in vitro exposure of **CpG**-ODN did not induce marked nitric oxide (NO) generation by macrophages, considerably enhanced amount of NO was generated by macrophages of **CpG**-ODN-treated animals. Their splenocytes

secreted soluble factors required for the induction of NO generation, and the increased NO generation was paralleled by an increase in antileishmanial activity. Inducible NO generation was suppressed by treating splenocyte supernatants with anti-IFN-gamma or anti-IL-12 antibodies, whereas in vivo administration of these anti-cytokine Ab along with **CpG**-ODN reversed protection against infection. **CpG** -ODN treatment resulted in reduced levels of IL-4, but increased levels of IFN-gamma, IL-12 and inducible NO synthase in infected spleen cells, which was magnified by encapsulation in mannose-coated liposomes. This targeted treatment was not only curative, but it also imparted resistance to reinfection. These results represent a general approach for intracellular targeting of **CpG**-ODN, which effectively enhances its therapeutic potential in redirecting curative **Th1** responses in **Th2** -driven disorders.

L8 ANSWER 20 OF 159 MEDLINE on STN
AN 2003103942 MEDLINE
DN PubMed ID: 12595427
TI Expression and immunogenicity of Mycoplasma hyopneumoniae heat shock protein antigen P42 by DNA vaccination.
AU Chen Ya-Lei; Wang Shao-Ning; Yang Wen-Jen; Chen Yi-Jiun; Lin Hsi-Hsun; Shiuan David
CS Department of Medical Technology, Fooying University, Kaohsiung, Republic of China.
SO Infection and immunity, (2003 Mar) 71 (3) 1155-60.
Journal code: 0246127. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200303
ED Entered STN: 20030306
Last Updated on STN: 20030321
Entered Medline: 20030320
AB Mycoplasma hyopneumoniae is the etiological agent of swine enzootic pneumonia, a chronic nonfatal disease affecting pigs of all ages. The goal of this study was to design DNA vaccines by constructing plasmid pcDNA3/P42, carrying the heat shock protein gene P42 of M. hyopneumoniae, and to evaluate the immune responses elicited in BALB/c mice. The expression of P42 was first examined in transfected NIH 3T3 cells by reverse transcription-PCR to ensure that the construct was functional. The humoral and cell-mediated immune responses induced by the plasmid were further evaluated in BALB/c mice through intramuscular injection. Both immunoglobulin G1 (IgG1) and IgG2a levels were 64 times those of the control groups during the first 8 weeks. The levels of interleukin-2 (IL-2), IL-4, and gamma interferon mRNAs in the immunized animals were elevated, and the proliferation of spleen cells was also enhanced in the immunized animals. The results indicate that pcDNA3/P42 DNA immunization induces both **Th1** and **Th2** immune responses. In addition, antiserum from the immunized animals was found to inhibit the growth of M. hyopneumoniae. The present study reveals that DNA vaccination could be a new strategy against infection by M. hyopneumoniae and may have potential for developing vaccines for other infectious diseases as well.

L8 ANSWER 21 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:857185 CAPLUS
DN 139:363533
TI HBsAg/HLA-A2 transgenic mice: A model for T cell tolerance to hepatitis B surface antigen in chronic hepatitis B virus infection
AU Loirat, D.; Mancini-Bourgine, M.; Abastado, J. -P.; Michel, M. -L.
CS Unite de Recombinaison et Expression Genetique/INSERM U163 and Unite de Carcinogenese Hepatique et Virologie Moleculaire/INSERM U370, Institut

Pasteur, Paris, 75 015, Fr.
SO International Immunology (2003), 15(10), 1125-1136
CODEN: INIMEN; ISSN: 0953-8178
PB Oxford University Press
DT Journal
LA English
AB A humanized murine model was developed to study T cell tolerance to the hepatitis B surface antigen (HBsAg) that is present in sera of hepatitis B virus chronic carriers. The HBsAg/HLA-A2 double-transgenic mice express a chimeric HLA-A2 MHC class I mol. and a high amount of the HBsAg in the liver that is secreted and present in sera during the animal's lifetime. In these mice, injection of plasmid DNA encoding HBsAg induced a high frequency of CD8+ T cells secreting IFN-γ in the periphery, with in vitro cytolytic activity and specificity for two dominant HBs-specific HLA-A2-restricted epitopes. Nevertheless, the DNA-based immunization elicited neither **Th1** nor **Th2** CD4+ T cell responses. Despite a high concentration of HBsAg in sera, these mice developed an immunocompetent CD8+ T cell repertoire towards the viral self-antigen, whereas the CD4+ T cell repertoire was tolerized. In the absence of a CD4+ T cell response, the IFN-γ-secreting CD8+ T cells primed by DNA-based immunization were unable to exert their antiviral functions in vivo on liver cells expressing the transgene product. However, when pro-inflammatory stimuli were given before or after DNA-based immunization, the HBsAg was cleared from the serum. This effect was antibody dependent and associated with the detection of an HBs-specific Th1 CD4+ T cell response in the periphery. This model provides evidence that HBsAg displayed a strong tolerogenic effect on the CD4+ T cell compartment that is associated with a defect in CD8+ T cell effector functions in vivo.
RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 22 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 13
AN 2003:302587 BIOSIS
DN PREV200300302587
TI Molecular approaches to disease control.
AU Babiuk, L. A. [Reprint Author]; Gomis, S.; Hecker, R.
CS Veterinary Infectious Disease Organization, 120 Veterinary Road, Saskatoon, SK, S7N 5E3, Canada
babiuk@sask.usask.ca
SO Poultry Science, (June 2003) Vol. 82, No. 6, pp. 870-875. print.
ISSN: 0032-5791 (ISSN print).
DT Article
LA English
ED Entered STN: 25 Jun 2003
Last Updated on STN: 25 Jun 2003
AB Recent advances in molecular biology, genomics, and immunology are revolutionizing our approach to managing infectious diseases of humans, livestock, and poultry. One of the most interesting additions to the armamentarium of research focusing on controlling infectious diseases has been a better understanding of how the host's innate immune system recognizes "danger" signals. Additionally, there has been recognition of the relationship between the innate and the specific arms of the immune system. For example, the recent discovery that **CpG** motifs can modulate immune responses has been used both as an adjuvant to enhance the responses to vaccines, as well as a direct immunostimulant to prevent infections. Using an Escherichia coli chicken model, we have been able to prevent cellulitis in chickens with **CpG** alone. Thus, **CpG** can be used immunoprophylactically to reduce infectious diseases. In addition, we will describe how **CpG** formulations with various antigens; recombinant proteins, peptides, and conventional vaccines can enhance immune responses to each of these different vaccine combinations. What is even more interesting is that **CpG**

incorporation in vaccines can shift the immune response from a predominant T helper 2 (Th2)-like immune response generally induced by killed or subunit proteins to a much more balanced **Th1-Th2** response. These immunomodulatory effects have significant implications for management of infectious diseases of all vertebrates.

L8 ANSWER 23 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 14
AN 2003:128502 BIOSIS
DN PREV200300128502
TI **CpG** penta- and hexadeoxyribonucleotides as potent immunomodulatory agents.
AU Bhagat, Lakshmi; Zhu, Fu-Gang; Yu, Dong; Tang, Jimmy; Wang, Hui; Kandimalla, Ekambar R.; Zhang, Ruiwen; Agrawal, Sudhir [Reprint Author]
CS Hybridon, Inc., 345 Vassar Street, Cambridge, MA, 02139, USA
sagrawal@hybridon.com
SO Biochemical and Biophysical Research Communications, (January 24 2003) Vol. 300, No. 4, pp. 853-861. print.
CODEN: BBRCA9. ISSN: 0006-291X.
DT Article
LA English
ED Entered STN: 5 Mar 2003
Last Updated on STN: 5 Mar 2003
AB We demonstrate a new design for immunomodulatory **CpG** DNA containing two sequences each with as few as five or six-nucleotides joined together via 3'-3' linkers. These do not require the -PuPu(Py)CGPyPy- hexameric motif generally found essential for **CpG** DNA immune stimulation. These novel, short-immunomers show potent immunostimulatory activity manifested by IL-12 and IL-6 secretion in murine spleen cell and PBMC cultures and splenomegaly in vivo. Short-immunomers show strong activation of NF-kappaB and stress-activated signaling pathways and induce cytokines in J774 cell cultures. The same sequences also induce cytokines in healthy human PBMC cultures whereas conventional **CpG** DNA requires different optimal sequences for murine and human immune cells. Additionally, short-immunomers inhibit IL-5 secretion and induce IFN-gamma secretion in conalbumin-sensitized mouse spleen cell cultures, suggesting reversal of established **Th2** responses to **Th1** type responses. Short-immunomer also inhibits growth of MCF-7 human tumor xenograft in nude mice. This is the first report of activity with such short DNA sequences and also of sequences lacking hexameric motifs proposed in earlier studies.

L8 ANSWER 24 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 15
AN 2003:377466 BIOSIS
DN PREV200300377466
TI Various factors (allergen nature, mouse strain, **CpG**/recombinant protein expressed) influence the immune response elicited by genetic immunization.
AU Chatel, J. M. [Reprint Author]; Song, L.; Bhogal, B.; Orson, F. M.
CS INRA-Laboratoire d'Immuno-Allergie Alimentaire, CE Saclay, DRM-SPI, Bat 136, 91191, Gif Sur Yvette, France
SO Allergy (Copenhagen), (July 2003) Vol. 58, No. 7, pp. 641-647. print.
CODEN: LLRGDY. ISSN: 0105-4538.
DT Article
LA English
ED Entered STN: 13 Aug 2003
Last Updated on STN: 13 Aug 2003
AB Background: Genetic immunization is a very promising therapeutic approach for allergy treatment. In the present study we investigate the influence of the nature of the allergen, the mouse strain, and the relative amount of **CpG** to expressed recombinant protein on immune responses using two major peanut allergens, Ara h 1 and Ara h 4. Methods: The cDNA

of Ara h 1 and of an isoform of Ara h 4 were cloned and inserted in pcDNA3. Antigen specific IgG1, IgG2a and IgE were followed after genetic immunization with 100 mug of these clones in mouse strain SKH-Hr1 or BALB/c and with 1 mug of the clones + 99 blank plasmid in SKH-Hr1. Results: Genetic immunization in SKH-Hr1 with Ara h 1 elicited a classical Th1 type response, but Ara h 4 elicited a mixed **Th1/Th2** response with high IgG1 and even IgE in some mice. In BALB/c both plasmids produced a high IgG1 level. Decreasing the amount of plasmid injected did not change the immune response profile. However, increasing the amount of **CpG** administered relative to the recombinant Ara h 4 protein expressed reversed the **Th1/Th2** response pattern in SKH-Hr1 mice. Conclusions: Immune responses after genetic immunization are strongly influenced by the nature of the allergen, the mouse strain, and the ratio of **CpG** to recombinant protein expressed.

L8 ANSWER 25 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 16
AN 2003:501352 BIOSIS
DN PREV200300503396
TI Ribavirin or **CpG** DNA sequence-modulated dendritic cells decrease the IgE level and airway inflammation.
AU Chiang, Dian-Jung; Ye, Yi-Ling; Chen, Wei-Li; Lee, Yueh-Lun; Hsu, Ni-Yun; Chiang, Bor-Luen [Reprint Author]
CS Department of Medical Research, National Taiwan University Hospital, Number 1, Chang-Teh Street, Taipei, 100, Taiwan
gicmbor@ha.mc.ntu.edu.tw
SO American Journal of Respiratory and Critical Care Medicine, (September 1 2003) Vol. 168, No. 5, pp. 575-580. print.
ISSN: 1073-449X (ISSN print).
DT Article
LA English
ED Entered STN: 29 Oct 2003
Last Updated on STN: 29 Oct 2003
AB Asthma is an allergic disease that is characterized by the imbalance between **Th1** and **Th2** cells and by the predominant Th2-type immune response. In this study, we investigated the application of dendritic cell (DCs)-based immunotherapy in modulating the immune response of allergic diseases. DCs incubated with ovalbumin (OVA), OVA plus ribavirin, OVA plus **CpG**-oligodeoxynucleotides (ODN 1826), or OVA plus non-**CpG**-ODN (ODN 1745) for 48 hours were injected intravenously into four corresponding groups of BALB/c mice. All of the mice were then immunized with OVA intraperitoneally 7 days later to establish an animal model of asthma. Serum levels of OVA antibody, airway hyperresponsivness, cell composition and cytokine levels in the bronchoalveolar lavage fluid, and cytokine profiles of spleen cells were analyzed. The data showed that ribavirin and ODN 1826 increased interleukin-12 synthesis and inhibited interleukin-10 production. ODN 1826 could also enhance the expression of B7.1, B7.2, major histocompatibility complex I, and major histocompatibility complex II molecules. Furthermore, the DCs modulated by ribavirin and ODN 1826 could downregulate the Th2-type immune response in vivo and could alleviate airway inflammation. This study elucidated the effect of ribavirin and **CpG**-ODN on DCs and demonstrated that in vitro modulated DCs might be a potential therapeutic approach for asthma.

L8 ANSWER 26 OF 159 MEDLINE on STN
AN 2003131415 MEDLINE
DN PubMed ID: 12645946
TI Kinetics and expression patterns of chemokine receptors in human CD4+ T lymphocytes primed by myeloid or plasmacytoid dendritic cells.
AU Langenkamp Anja; Nagata Kinya; Murphy Kristine; Wu Lijun; Lanzavecchia Antonio; Sallusto Federica

CS Institute for Research in Biomedicine, Bellinzona, Switzerland.
SO European journal of immunology, (2003 Feb) 33 (2) 474-82.
Journal code: 1273201. ISSN: 0014-2980.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200305
ED Entered STN: 20030321
Last Updated on STN: 20030502
Entered Medline: 20030501
AB We investigated the kinetics of expression of 12 chemoattractant receptors as a function of cell division following priming of human naive CD4+ T cells by different populations of dendritic cells (DC) and under conditions favoring **Th1** or **Th2** differentiation. Two chemokine receptors, CXCR3 and CXCR5, were rapidly up-regulated following T cell activation by either monocyte-derived DC, myeloid DC (mDC) or plasmacytoid DC (pDC). While CXCR5 expression was transient, expression of CXCR3 at advanced cell divisions was dependent on differentiation, being expressed at high levels on Th1 cells. Several other receptors (CCR2, CCR3, CCR4, CCR5, CXCR6 and CRTh2) were acquired progressively as a function of cell division and in a fashion that was influenced by polarizing cytokines. The Th2-associated chemoattractant receptors CRTh2 and CCR3 were up-regulated with slower kinetics compared to the Th1-associated receptors CXCR3 and CXCR6, consistent with a different kinetics and efficiency of polarization. Moreover, CCR4 and CXCR6 were preferentially induced in T cells activated by mDC and pDC, respectively. Finally, CXCR5 and CCR7 were also rapidly and transiently up-regulated in memory T cells following TCR stimulation. These results indicate a complex chemokine receptor regulation dependent on both T cell activation and differentiation state. In addition, they reveal the existence of DC-specific cues for the regulation of T cell migratory capacity.

L8 ANSWER 27 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 17
AN 2003:130972 BIOSIS
DN PREV200300130972
TI IL-4 regulates IL-12 p40 expression post-transcriptionally as well as via a promoter-based mechanism.
AU Seegmueller, Irene; Haecker, Hans; Wagner, Hermann [Reprint Author]
CS Institut fuer Medizinische Mikrobiologie, Immunologie und Hygiene, Trogerstrasse 9, 81675, Muenchen, Germany
h.wagner@lrz.tum.de
SO European Journal of Immunology, (February 2003) Vol. 33, No. 2, pp. 428-433. print.
ISSN: 0014-2980 (ISSN print).
DT Article
LA English
ED Entered STN: 12 Mar 2003
Last Updated on STN: 12 Mar 2003
AB IL-12 and IL-4, respectively, dominate **Th1** versus **Th2** polarization. Additionally IL-4 can inhibit IL-12 p40 production in DC. Here we show that macrophages respond to bacterial **CpG**-DNA with IL-12 p40 production in an IL-4-sensitive manner. Analysis of the molecular mechanism of this inhibition shows that IL-4 acts by reducing the stability of IL-12 p40 mRNA as well as by affecting promoter activity. IL-4 did not affect early **CpG**-DNA-induced signal transduction. However, IL-4 reduced the activity of the IL-12 p40 promoter and when de novo transcription of IL-12 p40 mRNA was blocked, IL-4 led to acceleration of IL-12 p40 mRNA degradation. These data show that IL-4 regulates IL-12 p40 expression by influencing promoter activity and by interfering with mRNA stability.

L8 ANSWER 28 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:896435 CAPLUS
DN 140:57926
TI T cell targeted allergen derivatives for improved efficacy and safety of specific immunotherapy for allergic disease
AU Gardner, Leanne M.; O'Hehir, Robyn E.; Rolland, Jennifer M.
CS Department of Pathology and Immunology, Monash University, Melbourne, Australia
SO Current Medicinal Chemistry: Anti-Inflammatory & Anti-Allergy Agents (2003), 2(4), 351-365
CODEN: CMCAGM; ISSN: 1568-0142
PB Bentham Science Publishers Ltd.
DT Journal; General Review
LA English
AB A review. Allergen-specific T cells play a pivotal role in initiating and regulating the immune response to allergens, with T cell targeted strategies showing promise for improved specific immunomodulation of the adverse immune response in allergic diseases. Atopic allergic individuals respond to allergen stimulation by dominant secretion of IL-4 and IL-5 (Th2-type cytokines) in contrast to non-atopic individuals where there is predominant IFN-γ secretion (Th1-type). Clin. effective, allergen-specific immunotherapy (SIT) is accompanied by altered allergen-specific T-cell response, notably cytokine changes of decreased IL-4 and IL-5 to IFN-γ ratio (**Th2/Th1**) and enhanced IL-10 secretion. Important contributing factors to these changes are likely to include the allergen concentration and form, adjuvants and antigen presenting cell type. Current regimens for SIT using high dose unfractionated allergen exts. injected incrementally via the s.c. route are limited by IgE-mediated adverse events, especially in asthmatic patients. Allergen derivs. with retained T cell reactivity but abrogated IgE binding should have higher efficacy and safety. Such derivs. include peptides containing dominant T cell epitopes of allergens and chemical-modified or recombinant mutant allergen mols. Both approaches have been evaluated successfully in vivo in animal models and limited clin. trials. Th1-inducing adjuvants including bacterial components or virus-like particles, and DNA vaccines may also promote repolarization of cytokine secretion from **Th2**-type to **Th1**-type but caution is needed as excessive IFN-γ secretion may invoke exuberant pathogenic inflammation. Alternative routes for allergen administration including intranasal, oral and sublingual are also under evaluation. Full elucidation of the mechanisms underlying safer, more effective SIT should facilitate wider clin. application in the treatment of allergic diseases and the availability of reliable laboratory assays for monitoring SIT efficacy based on T cell function.
RE.CNT 203 THERE ARE 203 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 29 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 18
AN 2003:541102 BIOSIS
DN PREV200300543864
TI T helper 2 immunity to hepatitis B surface antigen primed by gene-gun-mediated DNA vaccination can be shifted towards T helper 1 immunity by codelivery of **CpG** motif-containing oligodeoxynucleotides.
AU Zhou, X.; Zheng, L.; Liu, L.; Xiang, L.; Yuan, Z. [Reprint Author]
CS Key Laboratory of Medical Molecular Virology, Ministry of Education and Health Shanghai Medical College, Fudan University, 138 Yi Xue Yuan Road, Shanghai, 200032, China
zhyuan@shmu.edu.cn
SO Scandinavian Journal of Immunology, (September 2003) Vol. 58, No. 3, pp. 350-357. print.

ISSN: 0300-9475 (ISSN print).
DT Article
LA English
ED Entered STN: 19 Nov 2003
Last Updated on STN: 19 Nov 2003
AB Gene-gun-mediated DNA immunization usually induces predominant T helper 2 (Th2) type immune response. As oligodeoxynucleotides (ODN)-containing unmethylated **CpG** motifs can activate the innate immune system in a Th1-biased way, the potential of codelivery of **CpG** motifs-containing ODN (**CpG**-ODN) with plasmid DNA to switch the gene-gun-mediated Th2 immune response was evaluated in this study. Here we show that codelivery of **CpG**-ODN with plasmid DNA at certain ratio (10/1) can enhance the Th1 humoral and cell-mediated immune responses in gene-gun-mediated DNA immunization in BALB/c mice, including increasing the hepatitis B surface antigen-specific total immunoglobulin G (IgG), IgG2a subclass, cytotoxic T-cell lymphocyte activity as well as interferon-gamma (IFN-gamma) secretion. Taken together, these results demonstrate that codelivery of **CpG**-ODN with recombinant plasmid DNA by gene gun can shift the gene-gun-mediated DNA immune response from **Th2** towards **Th1**.

L8 ANSWER 30 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:290557 CAPLUS
DN 139:20716
TI Future prospect of DNA vaccine
AU Sato, Yukio; Kobayashi, Hiroko
CS School of Medicine, Second Dep. of Internal Medicine, Fukushima Prefectural Medical University, Japan
SO Arerugi, Men'eki (2003), 10(3), 294-301
CODEN: ARMEFS; ISSN: 1344-6932
PB Iyaku Janarusha
DT Journal; General Review
LA Japanese
AB A review discusses the antigen-specific immunotherapy for induction of Th1 type immune responses with immunostimulatory DNA sequence such as **CpG** in treatment of allergy.

L8 ANSWER 31 OF 159 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2003232128 EMBASE
TI Immunomodulation in asthma: Mechanisms and possible pitfalls.
AU Kay A.B.
CS A.B. Kay, Dept. of Allergy/Clinical Immunol., Imperial College London, National Heart and Lung Institute, Guy Scadding Bldg., Dovehouse St., London SW3 6LY, United Kingdom. a.b.kay@imperial.ac.uk
SO Current Opinion in Pharmacology, (2003) 3/3 (220-226).
Refs: 49
ISSN: 1471-4892 CODEN: COPUBK
PUI S 1471-4892(03)00038-9
CY United Kingdom
DT Journal; General Review
FS 015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Atopic diseases, including atopic asthma, are characterized by T helper cell (Th)2 cytokine pathology. The increased prevalence of asthma and allergic diseases, as well as Th1-associated conditions, is linked to 'excessive' hygiene. Several new immunomodulatory strategies in asthma and allergy, such as peptide therapy and DNA vaccines, show promise and are under clinical evaluation. They appear to exert their effects by producing

a **Th2** to **Th1** shift, as well as inducing regulatory cytokines such as interleukin-10 and transforming growth factor-β. There is no evidence that such approaches are associated with Th1 pathology in humans, although lung inflammation induced by Th1 cells has been observed in mice. IL-10 plays a key regulatory role in dampening both **Th2**- and **Th1**-associated diseases. Failure to stimulate regulatory responses could explain the rising trends in allergy and autoimmunity, and also partly explain the mode of action of allergen-injection immunotherapy and new immunomodulatory approaches.

L8 ANSWER 32 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 19
AN 2003:474533 BIOSIS
DN PREV200300474533
TI DNA immunostimulation: A novel therapeutic approach for allergic diseases.
Original Title: DNA-Immunstimulation: Ein neuer Ansatz zur Therapie allergischer Erkrankungen..
AU Petering, H. [Reprint Author]; Werfel, Th.; Kapp, A.
CS Klinik und Poliklinik fuer Dermatologie und Venerologie, Medizinische Hochschule Hannover, Ricklinger Strasse 5, D-30449, Hannover, Germany
SO Allergologie, (Mai 2003) Vol. 26, No. 5, pp. 202-211. print.
ISSN: 0344-5062 (ISSN print).
DT Article
General Review; (Literature Review)
LA German
ED Entered STN: 15 Oct 2003
Last Updated on STN: 15 Oct 2003
AB Some studies have linked the rise of atopy with an increase in living standards, immunization programs and antibiotic therapy. This has led to the theory that, while the normal response to childhood infections is the deviation of the immune system to a TH1-type cytokine response, the absence of these infections in industrialized countries has resulted in the predominance of an atopy-associated TH2-type response. Therefore, bacterial infections in childhood seem to have protective effects against a predominant TH2-type cytokine pattern, and immunostimulatory DNA sequences (**CpG** motifs) in bacterial DNA are gaining recognition as potential immunomodulators for switching on protective TH1-mediated immunity and preventing or potentially inhibiting TH2-dependent allergic responses. This review article starts with a description of the **TH1/TH2** paradigm as a conceptional framework for T helper cell differentiation in atopic disorders followed by an illustration of the structure of immunostimulatory DNA sequences and their effector functions on different cell types. In addition, this article provides insight into the potential therapeutic application of **CpG** -DNA in allergic diseases.

L8 ANSWER 33 OF 159 MEDLINE on STN DUPLICATE 20
AN 2003483257 MEDLINE
DN PubMed ID: 14561154
TI **CpG** oligodeoxynucleotides: a novel therapeutic approach for atopic disorders.
AU Hussain Iftikhar; Kline Joel N
CS Roy J. and Lucille A. Carver College of Medicine, University of Iowa, C33GH UIHC, 200 Hawkins Drive, Iowa City, IA 52242, USA.
SO Current drug targets. Inflammation and allergy, (2003 Sep) 2 (3) 199-205.
Ref: 80
Journal code: 101160019. ISSN: 1568-010X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals

EM 200311
ED Entered STN: 20031017
Last Updated on STN: 20031106
Entered Medline: 20031105
AB Atopic disorders such as allergic rhinitis, asthma and atopic dermatitis are associated with skewing of immune responses towards a TH2 phenotype, resulting in eosinophilic inflammation. TH2 cytokines promote eosinophil growth, migration and activation, mast cell differentiation, and IgE production, and are candidate mediators of pathologic abnormalities in asthma and other atopic diseases. There has been a significant increase in the prevalence of allergic disorders over the past several decades. Recent epidemiological studies suggest that reduced early-life exposure to strong TH1 stimuli in industrialized counties has skewed the **TH1** /**TH2** balance towards **TH2** responses. Improved hygiene, vaccination, and use of antibiotics may contribute to this imbalance. In the last half of the twentieth century we have seen the use of multiple agents to treat atopic disorders, ranging from antihistamines, steroids and leukotriene modifiers to anti-IgE antibodies. All these agents can block symptoms but do not significantly modify the course of the disease. Recent attempts to restore **TH1**/**TH2** balance by blocking **TH2** cytokines or inducing **TH1** cytokines, have not only failed to alter the outcome of atopic diseases but, in some cases, have caused significant adverse effects. An alternate method of suppressing TH2 responses takes advantage of the innate immune response to bacterial DNA. Oligodeoxynucleotides (ODN) containing sequence motifs centered on unmethylated CG dinucleotides (**CpG** ODN) resemble bacterial DNA, and like bacterial DNA are immunostimulatory; we and others have shown that **CpG** ODN can suppress TH2-mediated atopic inflammation without requiring the induction of TH1-type cytokines. These agents may represent a novel therapeutic approach toward restoring immune tolerance in atopic individuals.

L8 ANSWER 34 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 21
AN 2003:75331 BIOSIS
DN PREV200300075331
TI Flexibility of mouse classical and plasmacytoid-derived dendritic cells in directing T helper type 1 and 2 cell development: Dependency on antigen dose and differential Toll-like receptor ligation.
AU Boonstra, Andre [Reprint Author]; Asselin-Paturel, Carine; Gilliet, Michel; Crain, Chad; Trinchieri, Giorgio; Liu, Yong-Jun; O'Garra, Anne [Reprint Author]
CS Division of Immunoregulation, NIMR, The Ridgeway, Mill Hill, London, NW7 1AA, UK
andre.boonstra@nimr.mrc.ac.uk; aogarra@nimr.mrc.ac.uk
SO Journal of Experimental Medicine, (January 6 2003) Vol. 197, No. 1, pp. 101-109. print.
ISSN: 0022-1007 (ISSN print).
DT Article
LA English
ED Entered STN: 6 Feb 2003
Last Updated on STN: 6 Feb 2003
AB Distinct dendritic cell (DC) subsets have been suggested to be preprogrammed to direct either T helper cell (Th) type 1 or Th2 development, although more recently different pathogen products or stimuli have been shown to render these DCs more flexible. It is still unclear how distinct mouse DC subsets cultured from bone marrow precursors, blood, or their lymphoid tissue counterparts direct Th differentiation. We show that mouse myeloid and plasmacytoid precursor DCs (pDCs) cultured from bone marrow precursors and ex vivo splenic DC subsets can induce the development of both **Th1** and **Th2** effector cells depending on the dose of antigen. In general, high antigen doses induced Th1 cell development whereas low antigen doses induced Th2 cell

development. Both cultured and ex vivo splenic plasmacytoid-derived DCs enhanced CD4+ T cell proliferation and induced strong Th1 cell development when activated with the Toll-like receptor (TLR)9 ligand **CpG**, and not with the TLR4 ligand lipopolysaccharide (LPS). The responsiveness of plasmacytoid pDCs to **CpG** correlated with high TLR9 expression similarly to human plasmacytoid pDCs. Conversely, myeloid DCs generated with granulocyte/macrophage colony-stimulating factor enhanced Th1 cell development when stimulated with LPS as a result of their high level of TLR4 expression. Polarized Th1 responses resulting from high antigen dose were not additionally enhanced by stimulation of DCs by TLR ligands. Thus, the net effect of antigen dose, the state of maturation of the DCs together with the stimulation of DCs by pathogen-derived products, will determine whether a **Th1** or **Th2** response develops.

L8 ANSWER 35 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2003:140880 BIOSIS
DN PREV200300140880
TI The ability of murine dendritic cell subsets to direct T helper cell differentiation is dependent on microbial signals.
AU Manickasingham, Shivanthi P.; Edwards, Alexander D.; Schulz, Oliver; Sousa, Caetano Reis [Reprint Author]
CS Immunobiology Laboratory, Cancer Research UK, London Research Institute, Lincoln's Inn Fields Laboratories, 44 Lincoln's Inn Fields, London, WC2A 3PX, UK
caetano@cancer.org.uk
SO European Journal of Immunology, (January 2003) Vol. 33, No. 1, pp. 101-107. print.
ISSN: 0014-2980 (ISSN print).
DT Article
LA English
ED Entered STN: 19 Mar 2003
Last Updated on STN: 19 Mar 2003
AB Dendritic cells (DC) initiate T cell responses and direct the class of T cell immunity through the production of Th-polarizing cytokines. In the mouse, immunization with CD8alpha+ DC has led to Th1 priming whereas immunization with CD8alpha- DC has been associated with Th2 induction. Here, we use a direct T cell priming assay in vitro to re-examine the Th-directing potential of total DC or purified CD4+ DC, CD8alpha+ DC or CD4- CD8alpha- (double-negative; DN) DC subsets from mouse spleen. We show that the default Th effector phenotype induced by priming with DC depends on the protocol used for T cell purification, the T cell:antigen-presenting cell ratio and the antigen dose but is only marginally affected by DC subtype. All DC subsets can direct increased Th1 development in response to microbial stimuli known to elicit IL-12 production. Similarly, all subsets can suppress **Th1** development and allow **Th2** cells to expand upon exposure to IL-10-inducing microbial agents. The flexibility of DC in directing Th development in function of microbial signals argues against the notion of pre-determined "DC1" and "DC2" subsets and suggests that multiple DC subtypes can direct an appropriate Th response to different classes of infectious agents.

L8 ANSWER 36 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 22
AN 2003:95163 BIOSIS
DN PREV200300095163
TI Immunotherapy of allergic bronchopulmonary aspergillosis: A clinical and experimental approach.
AU Svirshchevskaya, E. V. [Reprint Author]; Kurup, V. P.
CS Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Miklukho-Maklaya St., 16/10, Moscow, 117997, Russia
esvir@mail.ibch.ru
SO Frontiers in Bioscience, (January 1 2003) Vol. 8, No. Cited January 3, 2003, pp. s92-s101. http://www.bioscience.org/. online.

ISSN: 1093-4715 (ISSN online).
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 12 Feb 2003
Last Updated on STN: 12 Feb 2003
AB Allergic bronchopulmonary aspergillosis (ABPA) is a severe allergic pulmonary complication caused by the saprophytic fungus Aspergillus fumigatus. The present review examines the pathogenesis of this disease describing in detail the role of innate and acquired immunity in the induction of sensitivity to A. fumigatus. Different approaches in developing specific immunotherapeutic treatments such as induction of anergy, regulatory cells, a switch from **Th2** to **Th1** type of immune response, **CpG** and genetic immunization and the usage of altered peptides or modified allergens are critically examined.

L8 ANSWER 37 OF 159 MEDLINE on STN DUPLICATE 23
AN 2003165417 MEDLINE
DN PubMed ID: 12683337
TI Up-to-date understanding of tuberculosis immunity.
AU Mitsuyama Masao; Akagawa Kiyoko; Kobayashi Kazuo; Sugawara Izamu; Kawakami Kazuyoshi; Yamamoto Saburo; Okada Zenshi
CS Department of Microbiology, Kyoto University Graduate School of Medicine, Yoshida-Konoecho, Sakyo-ku, Kyoto-shi, Kyoto 606-8501, Japan.. mituyama@mb.med.kyoto-u.ac.jp
SO Kekkaku : [Tuberculosis], (2003 Jan) 78 (1) 51-5. Ref: 0
Journal code: 0422132. ISSN: 0022-9776.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Japanese
FS Priority Journals
EM 200305
ED Entered STN: 20030410
Last Updated on STN: 20030521
Entered Medline: 20030520
AB This symposium was organized to provide the up-to-date knowledge on tuberculosis immunity, especially on the understanding of cytokines or Th1 cells involved in pathophysiology/protective immunity and vaccine development. Dr. Kazuo Kobayashi (Osaka City University) reported their findings on the immune response to bioactive lipid component from M. tuberculosis, trehalose-dimycolate (TDM) and sulfolipid (SL) in mice. Their unique and novel finding was that TDM is capable of inducing T-dependent immune response in euthymic mice. The specific immune response in TDM-immune mice was consisting of CD4+ cell response and expression of chemokines, inflammatory cytokines and then TH1-related cytokines. In contrast, SL did not show such an activity. TDM may be one of the protective antigens and may modulate the specific immune response of the host. Dr. Isamu Sugawara's group (JATA) has examined the involvement of various cytokines in the host response to aerosolic infection with virulent strain of M. tuberculosis by using cytokine-knockout mice. The single deletion of IFN-gamma or TNF alpha resulted in a severe lesion of multiple necrosis without granuloma, and cytokine mRNA level other than knocked out cytokine was normal, suggesting that IFN-gamma and TNF alpha are principally important cytokines. In knockout mice for IL-12 or IL-18, necrotic lesion was not induced after infection and the pathological change was not so significant as in IFN-gamma/TNF alpha knockout mice. By using IFN-gamma knockout mice, it became possible to generate a granulomatous lesion with central necrosis and cavity resembling the lesion in humans. These mouse model appeared to be useful in the analysis of pathophysiology of human tuberculosis. Dr. Kazuyoshi Kawakami (Ryukyu University) reported the importance of TH1 cytokines

in anti-tuberculous immunity. By using IL-12, IL-18 knockout mice or double knockout mice, it was shown that IL-12 exhibits more important role than IL-18 in the protection. A possible contribution of IL-23 was also suggested. In most of the clinical cases of tuberculosis, the production of IL-12, IL-18 and IFN-gamma is increased, however, the group of relatively lower cytokine production did not respond well to the treatment. In addition, the plasma level of one of the chemokines, IP-10, was shown to be an indicator for the severity of the disease. Thus, some cytokines appear to be employable for the novel treatment in the near future. Dr. Saburo Yamamoto (NIH) summarized the recent advance in the understanding of biological function of **CpG** motifs. Immunostimulatory DNA is effective in the modulation of **TH1/TH2** polarity and the enhancement of protective immunity to M. tuberulosis in animals. **CpG** motif (immunostimulatory DNA) appears to exert its activity by signaling cascade via TLR9 resulting in NF-kappa B activation and cytokine gene expression. Analysis of basic mechanism of action by **CpG** motif should pave the way to the clinical application in the future. Dr. Masaji Okada (Kinki Chuo Hospital) reported the current situation in the development of novel vaccines against tuberculosis. They have extensively constructed and examined the efficacy of various types of vaccines including subunit, DNA and recombinant BCG vaccines. Various vector systems have been tested for DNA vaccine. As immunizing antigens, a-Ag, ESAT-6, HSP65, 38kD-lipoprotein and so on have been employed. A large body of experimental data are accumulating for final evaluation, and among them, it is noteworthy to mention that HSP65DNA + IL-12DNA was 100 times more effective than conventional BCG in animal model. Among subunit vaccines, Mtb72f vaccine appears to be one of the promising candidates. In addition to the trial with various candidates, they have established a new mouse model, SCID/human PBL. This model animal has been employed for the development of vaccine effective for the induction of ESAT-6-specific human T cells.

L8 ANSWER 38 OF 159 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2003196194 EMBASE
TI [Immunostymulatory sequences of bacterial DNA (**CpG** DNA) - Connection with allergic diseases].
FRAGMENTY BAKTERYJNEGO DNA O WlASCIWOSCIACH IMMUNOMODULACYJNYCH (**CPG** DNA) - ZWIAZEK Z CHOROBAMI ALERGICZNYMI.
AU Chalubinski M.; Kowalski M.L.
CS M. Chalubinski, Kat. i Zakad Immunologii Klinicznej, Uniwersytetu Medycznego, ul. Pomorska 251, 92-213 Lodz, Poland
SO Alergia Astma Immunologia, (2003) 8/1 (1-7).
Refs: 60
ISSN: 1427-3101 CODEN: AAIMFF
CY Poland
DT Journal; General Review
FS 004 Microbiology
005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
LA Polish
SL English; Polish
AB The human and mammalian immune system has the ability to recognize the presence of bacterial DNA on the basis of recognition of **CpG** motifs (unmethylated cytidine-guanosine dinucleotides) within a particular base context. Several raports have shown that **CpG** motifs are both potent inducers of Th1-response that eliminates intracellular pathogenes and inhibitors of eosinophils and mast cells activation as well as IgE production, thus inhibiting Th2 type immune response characteristic for the allergic inflammation. It has been postulated that **CpG** DNA establishes **Th1/Th2** balance, supporting the

concept that the injection of allergen conjugated with appropriate **CpG** motifs may provide a novel immunotherapeutic approach for the treatment of allergic disorders.

L8 ANSWER 39 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:158347 CAPLUS
DN 138:236418
TI Interleukin-12: Potential role in asthma therapy
AU Leonard, Patricia; Sur, Sanjiv
CS Department of Allergy and Immunology, University of Texas Medical Branch, Galveston, TX, USA
SO BioDrugs (2003), 17(1), 1-7
CODEN: BIDRF4; ISSN: 1173-8804
PB Adis International Ltd.
DT Journal; General Review
LA English
AB A review. Asthma is an inflammatory disease of the airways leading to morbidity and mortality. With advances in the understanding of the mol. and cellular mechanisms involved in the asthmatic response, researchers have identified specific mediators that may be targeted to control the inflammatory state of asthma. The Th2 hypothesis proposes that the inflammation in asthma arises from an imbalance between the 2 CD4+ T lymphocyte subsets, T helper (Th) type 1 and Th2. Th2 cells release many cytokines that have been shown to regulate the inflammatory response, while the Th1 cytokines counteract this response. The Th1 cytokine, interleukin (IL)-12, has been a target of intense study because it mediates the Th1 response and offers a means of modifying the asthmatic inflammatory response. Numerous murine studies have shown that this cytokine can potently inhibit allergic airway inflammation in asthma. Inhalation of IL-12 has been shown to increase its efficacy in inhibiting allergic inflammation in murine models while decreasing adverse effects seen with systemic administration of this cytokine. However, an initial study of inhaled IL-12 in humans with asthma was terminated because of adverse effects. The use of systemically administered IL-12 in patients with asthma has been limited due to cytokine toxicity. Another treatment option that has the potential of inducing a Th1 cytokine response is the use of IL-12 linked to polyethylene glycol (PEG) moieties. This mode of administration is likely to enhance cytokine delivery to the target organ, while decreasing its toxicity. IL-12 gene therapy has also been examined as a means of suppressing airway hyperreactivity in murine asthma, but its potential in human asthma has not been explored. Several recent studies have investigated the role of **CpG** DNA motifs as endogenous inducers of IL-12 with encouraging results in both mice and humans. These studies may result in novel Th1-inducing **CpG**-based immunotherapies for asthma.
RE.CNT 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 40 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2003:568684 BIOSIS
DN PREV200300563544
TI THE ROLE OF DENDRITIC CELLS IN IBD.
AU Thompson-Snipes, LuAnn [Reprint Author]; Cox, Bettye [Reprint Author]; Carter, Lisa [Reprint Author]; Chen, Lei [Reprint Author]; Finegold, Milton [Reprint Author]
CS Houston, TX, USA
SO Digestive Disease Week Abstracts and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. W1123. e-file.
Meeting Info.: Digestive Disease 2003. FL, Orlando, USA. May 17-22, 2003. American Association for the Study of Liver Diseases; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
DT Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 3 Dec 2003
Last Updated on STN: 3 Dec 2003
AB We hypothesize that dendritic cells (DCs), as immune regulatory cells, are critically important in the pathogenesis of IBD. We have chosen to use the Galphai2 deficient (-/-) mouse model of IBD to study the role of DCs in colitis. In a conventional mouse facility, all Galphai2-/- 129/SvEv mice develop colitis, whereas all Galphai2-/- C57BL/6 mice remain healthy. The genetic background is important in disease progression indicating the presence of a number of modifier genes for Galphai2-/- colitis. Loss of tolerance to intestinal flora is one major event that could lead to colitis in the Galphai2-/- mouse. In this study we are comparing DCs isolated from 129/SvEv mice and C57BL/6 mice. We have examined cytokine production by splenic DCs isolated from wild type (wt) and Galphai2-/- mice on the 129/SvEv and C57BL/6 background. Methods: Dendritic cells were enriched from spleens or mesenteric lymph nodes (MLN) by a StemSep negative selection system (StemCell Inc., Vancouver, B.C.). Cells were cultured at 106 cells/ml in microtiter plates with IL-4 and GM-CSF (1000 U/ml each) for 18 hours with either media alone, 1 ng/ml LPS or 4 mg/ml **CpG** motifs. Supernatants were collected and assayed for pro-inflammatory and **TH1**/**TH2** murine cytokines using the Luminex LapMap 100 system. DCs enriched from MLN were analyzed by fluorometry (FACS) after labeling with a panel of antibodies conjugated with FITC, PE or PerCp-Cy5. Results: When splenic DCs are incubated for 18 hours with IL-4, GM-CSF with and without LPS or **CpG**, we find that DCs from 129/SvEv Galphai2-/- mice have an attenuated production of IL-10 in response to LPS or CpGs stimulation compared to wt 129/SvEv, wt C57BL/6, or Galphai2-/- C57BL/6 mice. This suggests a reduced capacity of 129/SvEv Galphai2-/- DCs to maintain tolerance. We also observe a significant difference in both IL-12p70 and IL-6 in response to either low LPS or **CpG** in the 129Sv/Ev strain relative to the C57BL/6 Galphai2-/-t mice. Comparing DCs from MLN of wt and Galphai2-/- 129/SvEv mice, we find major differences in expression of the co-stimulatory molecule, B7-2, a potent activator of T, B and NK-cells. Normal mice have more CD11c+/CD11b+/B7-2+ cells (mature phenotype) than the Galphai2-/- mice. Conversely, the Galphai2-/- mice have more CD11c+CD11b-DEC-205+ cells than the normal mice. These observations are consistent with the hypothesis that the Galphai2-/- DCs are less mature and can more readily take up antigen for presentation to T-cells and B-cells. We conclude that there are major functional differences in DCs in mice susceptible to IBD..

L8 ANSWER 41 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 24
AN 2003-140201 [13] WPIDS
DNN N2003-111462 DNC C2003-035456
TI Compositions for treating **Th1**/**Th2** cell-related diseases comprise interleukin-2 or 4 and stromal cell-derived factor-1 alpha, their modulators, modulators of tyrosine kinase Syk, ZAP-70 and nuclear factor of activated T cells.
DC B04 C06 D16 S03
IN JINQUAN, T; POULSEN, L K
PA (ALKA-N) ALK-ABELLO AS
CYC 101
PI WO 2002089832 A2 20021114 (200313)* EN 77
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003103938 A1 20030605 (200339)

EP 1418936 A2 20040519 (200433) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR

ADT WO 2002089832 A2 WO 2002-DK295 20020507; US 2003103938 A1 Provisional US 2001-289711P 20010509, US 2002-143528 20020509; EP 1418936 A2 EP 2002-724144 20020507, WO 2002-DK295 20020507

FDT EP 1418936 A2 Based on WO 2002089832

PRAI US 2001-289711P 20010509; DK 2001-726 20010509; US 2002-143528 20020509

AB WO 200289832 A UPAB: 20030224

NOVELTY - Compositions (C1) and (C2) comprising:

(a) Interleukin-4 (IL-4) (C1)/IL-2 (C2) and stromal cell-derived factor-1 alpha (SDF-1 alpha) (SF);

(b) IL-4 (C1)/IL-2 (C2) stimulant and stimulant of SF;

(c) Antagonist (Ant) of IL-2 (C1)/Ant of IL-4 (C2) and Ant of SF;

(d) Inhibitor (C1)/stimulant (C2) of Syk or NFAT1;

(e) Stimulant (C1)/inhibitor (C2) of ZAP-70 or NFAT2; or

(f) IL-4 (C1)/IL-2 (C2) stimulating adjuvant and SF, are new.

DETAILED DESCRIPTION - Compositions (C1) and (C2) comprise active substances selected from:

(a) Interleukin-4 (IL-4) (C1) or IL-2 (C2) and stromal cell-derived factor-1 alpha (SDF-1 alpha);

(b) IL-4 (C1) or IL-2 (C2) stimulant and stimulant of SDF-1 alpha ;

(c) Antagonist of IL-2 (C1) or antagonist of IL-4 (C2) and antagonist of SDF-1 alpha ;

(d) Inhibitor (C1) or stimulant (C2) of Syk or NFAT1;

(e) Stimulant (C1) or inhibitor (C2) of ZAP-70 or NFAT2;

(f) IL-4 (C1) or IL-2 (C2) stimulating adjuvant and SDF-1 alpha ;

(g) A functional derivative, analogue or part of any of the substances (a)-(f); or

(h) a combination of any of the substances relative to (C1) or (C2).

INDEPENDENT CLAIMS are also included for the following:

(1) an antisense peptide nucleic acid (APNA) that is complementary to a DNA molecule encoding the tyrosine kinase Syk or ZAP-70 or its part for preventing or treating a **Th1**/**Th2** cell-related disease by modulating **Th1**/**Th2** ratio;

(2) Evaluating (M1) the T helper cell profile comprising obtaining a T helper cell containing sample, measuring the level of phosphorylated Syk, phosphorylated ZAP-70, intranucleic NFAT1 and/or intranucleic NFAT2 and using the measuring results obtained to assess the **Th1**/**Th2** level;

(3) Testing (M2) the effect of a product or a method on the **Th1**/**Th2** ratio comprising obtaining a T helper cell containing culture with a known **Th1**/**Th2** ratio, subjecting the T helper cells to the product or method, measuring the level of phosphorylated Syk, phosphorylated ZAP-70, intranucleic NFAT1 and/or intranucleic NFAT2 in the sample and using the measuring results obtained to assess the **Th1**/**Th2** level;

(4) Diagnostic test kit comprising one or more probes specific for binding to phosphorylated Syk, phosphorylated ZAP-70, intranucleic NFAT1 and/or intranucleic NFAT2 and optionally a detection system; and

(5) Producing (M3) a culture enriched in **Th1**/**Th2** cells by obtaining a T helper cell containing sample, subjecting the sample to an active substance as in (C1) and (C2) to modulate the **Th1**/**Th2** ratio.

ACTIVITY - Immunosuppressive; Cytostatic; Antiallergic; Antipyretic; Antiasthmatic; Ophthalmological; Antiinflammatory; Antiulcer; Nephrotropic; Dermatological; Antirheumatic; Antiarthritic; Antidiabetic; Antithyroid; Cardiant.

No biological data available.

MECHANISM OF ACTION - Modulator of IL-4/IL-2, SDF-1 alpha , Syk, ZAP-70, NFAT1 or NFAT2 (all claimed); Antisense therapy.

Intracellular **Th1** and **Th2** cytokine was detected

by flow cytometry. The CB T cells were stimulated with different combinations among interleukin-2 (IL-2) (10 ng/ml), IL-4 (10 ng/ml), and SDF-1 alpha (100 ng/ml), before intracellular cytokine assay. **Th1** and **Th2** cytokines assayed were interferon gamma (IFN- gamma), IL-4 or IFN- gamma and IL-4. The CD4+T cells from normal CB seem to be undifferentiated and unprimed showing naive Th pattern. In freshly isolated CB CD4+ T cells IFN- gamma and IL-4 double positive were 9.7%, whereas, IFN- gamma or IL-4 single positive were 8.5% or 12.1%, respectively. After 8 days of stimulation with IL-2 and SDF-1 alpha , the cells were switched to Th1 pattern in terms of expression of IFN- gamma (84%), whereas the stimulation with IL-4 an SDF-1 alpha lead the CBT cells to express Th2 pattern (90.3%). None of IL-2, IL-4 and SDF- alpha alone nor combination of IL-2 and IL-4 showed such function (data not shown). No significant difference was seen in terms of cellular proliferation between CB CD4+ T cells cultured without stimulus within 8 days as detected by (3H)thymidine incorporation into DNA assay. The cells cultured without stimulation had no significant change in terms of expression of intracellular cytokines during 8 days (data not shown). CXCR4 (CXC receptor 4) monoclonal antibody (mAb) significantly blocked such on-switch, whereas isotype Ig did not.

USE - (C1) and (C2) are useful for preventing or treating, respectively, a **Th1/Th2** cell-related disease in a human or animal by reducing/increasing the **Th1/Th2** ratio, respectively. (C1) and (C2) further comprise a pathogenic substance eliciting the **Th1/Th2**-related disease to be treated.
In (C1), the pathogenic substance is an infectious agent eliciting an infectious disease, or is an antigen, especially an autoantigen eliciting an autoimmune disease, or hapten or an allergen eliciting a delayed type hypersensitivity. In (C2) the pathogenic substance is a parasite organism or its portion, an antigen, preferably an allergen eliciting an allergic disease

Specifically, (C1) is useful for treating or preventing **Th1** or **Th2** cell-related diseases such as infectious disease, autoimmune disease, delayed type hypersensitivity, cancer, in a human or animal. (C2) is useful for treating or preventing a Th2 cell-related disease such as an allergic disease including hay fever, rhinoconjunctivitis, rhinitis and asthma, and also cancer.

(C1) and (C2) are either administered to the subject or T helper cells are removed from a subject and contacted ex vivo with the compositions.

Treatment may further comprise a second treatment involving the manipulation of the immune system such as vaccination, antigen specific immunotherapy, allergen specific immunotherapy, nonspecific immunotherapy or organ transplantation. APNA is useful in the manufacture of a medicament or for preventing or treating a Th1 or Th2 cell-related disease.

Cultures produced in (M3) are useful for in vitro or in vivo research and experiments (all claimed).

The autoimmune diseases treatable include encephalomyelopathic diseases, demyelinating and other autoimmune diseases such as multiple sclerosis, pneumonitis, sarcoidosis, ulcerative colitis, whipple's disease, vasculitis syndrome, Goodpastures syndrome, acute glomerulonephritis, gastrointestinal diseases such as Crohn's disease, skin diseases such as psoriasis, allergic skin disease, atopic dermatitis, joint diseases such as rheumatoid arthritis, musculoskeletal diseases such as myasthenia gravis, endocrine diseases such as insulin dependent diabetes mellitus, autoimmune thyroiditis, hyperthyroidism, cardiovascular diseases such as cardiomyopathy, vasculitis, cardiovascular disease associated with systemic diseases such as systemic lupus erythematosus, scleroderma, and polyarthritis nodosa.
Dwg.0/4

L8 ANSWER 42 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE

25
AN 2003-447327 [42] WPIDS
DNC C2003-118768
TI Modulating immune responses in a mammal with a bladder disorder e.g. bladder cancer, by administering nucleic acids comprising un-methylated **CpG** sequences, nucleic acids encoding alpha-MSH, or alpha-MSH peptides to the mammal.
DC B04 D16
IN HEDLEY, M L
PA (HEDL-I) HEDLEY M L
CYC 1
PI US 2002193332 A1 20021219 (200342)* 17
ADT US 2002193332 A1 Provisional US 2001-268175P 20010212, US 2002-74956 20020212
PRAI US 2001-268175P 20010212; US 2002-74956 20020212
AB US2002193332 A UPAB: 20030703
NOVELTY - Modulating an immune response in a mammal, comprises identifying a mammal that has or is at risk for having a bladder disorder, and administering:

(a) an isolated nucleic acid (N1) comprising an un-methylated **CpG** sequence to the mammal;

(b) an isolated nucleic acid (N2) comprising sequence encoding alpha -MSH to the mammal; or

(c) a peptide (P) that binds to a melanocortin receptor to the mammal.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for an isolated nucleic acid comprising an un-methylated **CpG** sequence and a sequence encoding alpha -MSH. The un-methylated **CpG** sequence comprises an immunostimulatory sequence. Alpha-MSH is an antiinflammatory peptide of sequence (A1):

Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val (A1)

ACTIVITY - Cytostatic; Antiinflammatory.

No biological data given.

MECHANISM OF ACTION - Immune response modulator; Inhibitor of histamine release from master cells; Inhibitor of neutrophil chemotaxis and/or migration to inflamed sites; Inhibitor of macrophage activation; Inhibitor of expression of co-stimulatory factors by dendritic cells.

USE - The method is useful for modulating immune response in a mammal having a bladder disorder, where administration of (N1) results in an amelioration of one or more symptoms of the disorder. Preferably, the method is useful for modulating immune response in a mammal having bladder cancer (where administration of (N1) results in a decrease in tumor size or activity), or for modulating immune response in a mammal having interstitial cystitis (where administration of (N1) results in a modulation of the immune response from **Th2** response to a **Th1** response). The method is also useful for modulating immune response in a mammal having bladder disorder that is characterized by inflammation which is associated with symptoms of interstitial cystitis or associated with a disruption of the integrity of the bladder lining (claimed).

Dwg.0/4

L8 ANSWER 43 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 26
AN 2003:33924 BIOSIS
DN PREV200300033924
TI DNA vaccination with heat shock protein 60 inhibits cyclophosphamide-accelerated diabetes.
AU Quintana, Francisco J.; Carmi, Pnina; Cohen, Irun R. [Reprint Author]
CS Department of Immunology, Weizmann Institute of Science, Rehovot, 76100, Israel
irun.cohen@weizmann.ac.il
SO Journal of Immunology, (November 15 2002) Vol. 169, No. 10, pp. 6030-6035.

print.
ISSN: 0022-1767 (ISSN print).
DT Article
LA English
ED Entered STN: 8 Jan 2003
Last Updated on STN: 8 Jan 2003
AB Nonobese diabetic (NOD) mice spontaneously develop diabetes as a consequence of an autoimmune process that can be inhibited by immunotherapy with the 60-kDa heat shock protein (hsp60), with its mycobacterial counterpart 65-kDa (hsp65), or with other Ags such as insulin and glutamic acid decarboxylase (GAD). Microbial infection and innate signaling via LPS or **CpG** motifs can also inhibit the spontaneous diabetogenic process. In addition to the spontaneous disease, however, NOD mice can develop a more robust cyclophosphamide-accelerated diabetes (CAD). In this work, we studied the effect on CAD of DNA vaccination with constructs encoding the Ags human hsp60 (phsp60) or mycobacterial hsp65 (phsp65). Vaccination with phsp60 protected NOD mice from CAD. In contrast, vaccination with phsp65, with an empty vector, or with a **CpG**-positive oligonucleotide was not effective, suggesting that the efficacy of the phsp60 construct might be based on regulatory hsp60 epitopes not shared with its mycobacterial counterpart, hsp65. Vaccination with phsp60 modulated the T cell responses to hsp60 and also to the GAD and insulin autoantigens; T cell proliferative responses were significantly reduced, and the pattern of cytokine secretion to hsp60, GAD, and insulin showed an increase in IL-10 and IL-5 secretion and a decrease in IFN-gamma secretion, compatible with a shift from a **Th1**-like toward a **Th2**-like autoimmune response. Our results extend the role of specific hsp60 immunomodulation in the control of beta cell autoimmunity and demonstrate that immunoregulatory networks activated by specific phsp60 vaccination can spread to other Ags targeted during the progression of diabetes, like insulin and GAD.

L8 ANSWER 44 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 27
AN 2002:359091 BIOSIS
DN PREV200200359091
TI Plasmid DNA encoding IFN-gamma-inducible protein 10 redirects antigen-specific T cell polarization and suppresses experimental autoimmune encephalomyelitis.
AU Wildbaum, Gizi; Netzer, Nir; Karin, Nathan [Reprint author]
CS Rappaport Family Institute for Research in the Medical Sciences, Bruce Rappaport Faculty of Medicine, Technion, P.O. Box 9697, Haifa, 31096, Israel
nkarin@tx.technion.ac.il
SO Journal of Immunology, (June 1, 2002) Vol. 168, No. 11, pp. 5885-5892. print.
CODEN: JOIMA3. ISSN: 0022-1767.
DT Article
LA English
ED Entered STN: 26 Jun 2002
Last Updated on STN: 26 Jun 2002
AB IFN-gamma-inducible protein 10 (IP-10) is a CXC chemokine that stimulates the directional migration of activated T cells, particularly Th1 cells. We demonstrate in this work that during activation this chemokine drives naive CD4+ T cells into Th1 polarization. Administration of plasmid DNA encoding self IP-10 was found capable of breaking down immunological tolerance to IP-10, resulting in the generation of self-specific immunity to the gene product of the vaccine. Despite the **CpG** motif that drives T cells into Th1, the vaccine redirected the polarization of myelin basic protein-specific T cells into Th2 and conferred the vaccinated recipients a high state of resistance against experimental autoimmune encephalomyelitis, a T cell-mediated autoimmune disease of the CNS. The vaccine also suppressed full-blown ongoing disease in a mouse model of

multiple sclerosis. Self-specific Ab to IP-10 developed in protected animals could inhibit leukocyte migration, alter the in vitro **Th1** /**Th2** balance of autoimmune T cells, and adoptively transfer disease suppression. This demonstrates not only the pivotal role of a chemokine in T cell polarization and function but also its potential implications for plasmid DNA gene therapy.

L8 ANSWER 45 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2003:11295 BIOSIS
DN PREV200300011295
TI Novel nutritional strategies for skewing the immune system from **Th2** to **Th1**: Implications for cancer prevention and cancer treatment.
AU Fasy, T. M. [Reprint Author]; Wang, L.-H. [Reprint Author]; Sun, A. S.
CS Mount Sinai School of Medicine, New York, NY, USA
SO Journal of Nutrition, (November 2002) Vol. 132, No. 11 Supplement, pp. 3545S. print.
Meeting Info.: International Research Conference on Food, Nutrition and Cancer. Washington DC, USA. July 11-12, 2002. American Society for Nutritional Sciences.
ISSN: 0022-3166 (ISSN print).
DT Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 18 Dec 2002
Last Updated on STN: 18 Dec 2002

L8 ANSWER 46 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 28
AN 2002:552550 BIOSIS
DN PREV200200552550
TI Liposomal immunostimulatory DNA sequence (**ISS**-ODN): An efficient parenteral and mucosal adjuvant for influenza and hepatitis B vaccines.
AU Joseph, Aviva; Louria-Hayon, Igal; Plis-Finarov, Alla; Zeira, Evelyne; Zakay-Rones, Zichria; Raz, Eyal; Hayashi, Tomoko; Takabayashi, Kenji; Barenholz, Yechezkel; Kedar, Eli [Reprint author]
CS Lautenberg Center for General and Tumor Immunology, Medical School, Hebrew University-Hadassah, P.O. Box 12272, Jerusalem, 91120, Israel
kedar@md.huji.ac.il
SO Vaccine, (10 September, 2002) Vol. 20, No. 27-28, pp. 3342-3354. print.
CODEN: VACCDE. ISSN: 0264-410X.
DT Article
LA English
ED Entered STN: 30 Oct 2002
Last Updated on STN: 30 Oct 2002
AB Synthetic oligodeoxynucleotides (ODNs) containing immunostimulatory sequences (**ISS**-ODN, also known as **CpG**-ODNs) have been shown to display in experimental models potent Th1-biassed immunoadjuvant activity upon parenteral or mucosal co-administration with a variety of antigens. In an attempt to potentiate adjuvant activity, and to reduce dose and number of administrations, **ISS**-ODN was entrapped (up to 90% efficiency) in large (1.5 mum) multilamellar liposomes using a simple and fast (5 min) procedure. Mice were vaccinated once or twice intramuscularly (i.m.) or intranasally (i.n.) with subunit influenza vaccines (consisting of the viral hemagglutinin and neuraminidase, HN) or with hepatitis B surface antigen particles (HBsAg), either non-encapsulated or liposome-encapsulated, together with free or liposomal **ISS**-ODN (5-25 mug per dose). At 3-12 weeks post-vaccination, the humoral (systemic, mucosal) and cellular responses and protective immunity were assessed. Vaccine formulations containing liposomal **ISS** -ODN co-administered with either soluble antigen or liposomal antigen (in the same vesicles or in separate vesicles) were up to 30 times more

effective than formulations containing un-encapsulated **ISS**-ODN in inducing: (a) antigen-specific serum and mucosal IgG2a and IgA antibodies; (b) splenocyte proliferative response, cytotoxic activity and IFNgamma production; (c) a DTH response; and (d) protection against virus challenge. The response was Th1-dominant in the influenza model and a mixed **Th1+Th2** response in the hepatitis B model. No adverse reactions were noted. Thus, liposomal encapsulation of **ISS**-ODN further enhances its inherent adjuvant activity.

L8 ANSWER 47 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 29
AN 2002:517712 BIOSIS
DN PREV200200517712
TI Gene gun bombardment with gold particles displays a particular Th2-promoting signal that over-rules the Th1-inducing effect of immunostimulatory **CpG** motifs in DNA vaccines.
AU Weiss, Richard; Scheiblhofer, Sandra; Freund, Johann; Ferreira, Fatima; Livey, Ian; Thalhamer, Josef [Reprint author]
CS Institute of Chemistry and Biochemistry, University of Salzburg, Hellbrunner Street 34, A-5020, Salzburg, Austria
josef.thalhamer@sbg.ac.at
SO Vaccine, (19 August, 2002) Vol. 20, No. 25-26, pp. 3148-3154. print.
CODEN: VACCDE. ISSN: 0264-410X.
DT Article
LA English
ED Entered STN: 9 Oct 2002
Last Updated on STN: 9 Oct 2002
AB The mode of administering a DNA vaccine can influence the type of immune response induced by the vaccine. For instance, application of a DNA vaccine by gene gun typically induces a Th2-type reaction, whereas needle inoculation triggers a Th1 response. It has been proposed that the approximately 100-fold difference in the amount of DNA administered by these two methods is the critical factor determining whether a **Th1** or a **Th2** response is made. To test this hypothesis, BALB/c mice were immunized with two plasmid DNA constructs encoding different proteins (OspC/ZS7 of Borrelia burgdorferi and Bet v 1a, the major birch pollen allergen). Both vaccines were applied by needle and/or by gene gun immunization at the same and at different sites of injection. An analysis of the IgG subclass distribution and measurement of IFN-gamma after antigen-specific lymphoproliferation does not support the widely accepted view that Th2-type immunity induced by gene gun application is solely due to the low amount of injected plasmid DNA thus falling below the critical concentration of **CpG** motifs necessary for Th1-induction. Furthermore, the data also indicate a strong and even systemic adjuvant effect of the gene gun shot itself.

L8 ANSWER 48 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 30
AN 2002:296996 BIOSIS
DN PREV200200296996
TI Recombinant Ochrobactrum anthropi expressing Brucella abortus Cu,Zn superoxide dismutase protects mice against B. abortus infection only after switching of immune responses to Th1 type.
AU He, Yongqun; Vemulapalli, Ramesh; Schurig, Gerhardt G. [Reprint author]
CS Center for Molecular Medicine and Infectious Diseases, Department of Biomedical Sciences and Pathobiology, VA-MD Regional College of Veterinary Medicine, Virginia Polytechnic Institute and State University, 1410 Prices Fork Rd., Blacksburg, VA, 24061-0342, USA
gschurig@vt.edu
SO Infection and Immunity, (May, 2002) Vol. 70, No. 5, pp. 2535-2543. print.
CODEN: INFIBR. ISSN: 0019-9567.
DT Article
LA English

ED Entered STN: 15 May 2002
Last Updated on STN: 15 May 2002
AB The members of the genus Brucella are gram-negative, facultatively intracellular bacterial pathogens that cause brucellosis in many animal species and humans. Although live, attenuated vaccines are available to protect several animal species from the disease, there is no safe and effective vaccine for human use. Here we report that a bacterium that is closely related to Brucella species, Ochrobactrum anthropi, can be used as a vaccine vector for the delivery of Brucella antigens to mice, leading to the elicitation of protective immunity against brucellosis. Brucella abortus Cu,Zn superoxide dismutase (SOD), a protective Brucella antigen, was expressed in large amounts in O. anthropi strain 49237 by use of the broad-host-range plasmid pBBR1MCS. Neither O. anthropi strain 49237 nor the recombinant O. anthropi strain 49237SOD, expressing B. abortus Cu,Zn SOD, provided protection against virulent Brucella infection in mice. Analysis of immune responses indicated that strains 49237 and 49237SOD stimulated a mix of **Th1** and **Th2** type responses in the mice. After the immune response was switched to a Th1-biased response by addition of oligonucleotides containing unmethylated **CpG** motifs, both O. anthropi strain 49237 and the recombinant O. anthropi strain 49237SOD induced protection in mice. However, the protection conferred by strain 49237SOD was significantly better than that induced by the parental strain, 49237.

L8 ANSWER 49 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 31
AN 2002:481469 BIOSIS
DN PREV200200481469
TI DNA methylation changes at human Th2 cytokine genes coincide with DNase I hypersensitive site formation during CD4+ T cell differentiation.
AU Santangelo, Samantha; Cousins, David J.; Winkelmann, Nicole E. E.; Staynov, Dontcho Z. [Reprint author]
CS Department of Respiratory Medicine and Allergy, King's College, Guy's Hospital, Fifth Floor Thomas Guy House, London, SE1 9RT, UK
dontcho.staynov@kcl.ac.uk
SO Journal of Immunology, (August 15, 2002) Vol. 169, No. 4, pp. 1893-1903. print.
CODEN: JOIMA3. ISSN: 0022-1767.
DT Article
LA English
ED Entered STN: 11 Sep 2002
Last Updated on STN: 11 Sep 2002
AB The differentiation of naive CD4+ T lymphocytes into **Th1** and **Th2** lineages generates either cellular or humoral immune responses. Th2 cells express the cytokines IL-4, -5, and -13, which are implicated in asthma and atopy. Much has been published about the regulation of murine Th2 cytokine expression, but studies in human primary T cells are less common. We have developed a method for differentiating human CD45RA+ (naive) T cells into **Th1** and **Th2** populations that display distinct cytokine expression profiles. We examined both **CpG** methylation, using bisulfite DNA modification and sequencing, and chromatin structure around the IL-4 and IL-13 genes before and after human T cell differentiation and in normal human skin fibroblasts. In naive cells, the DNA was predominantly methylated. After Th2 differentiation, DNase I hypersensitive sites (DHS) appeared at IL-4 and IL-13 and **CpG** demethylation occurred only around the Th2-specific DHS. Both DHS and **CpG** demethylation coincided with consensus binding sites for the Th2-specific transcription factor GATA-3. Although fibroblasts, like naive and Th1 cells, did not express IL-4 or IL-13, DHS and unmethylated **CpG** sites that were distinct from the Th2-specific sites were observed, suggesting that chromatin structure in this cluster not only varies in T cells according to IL-4/IL-13 expression but is also tissue specific.

L8 ANSWER 50 OF 159 MEDLINE on STN
AN 2002393229 MEDLINE
DN PubMed ID: 12133976
TI Long-term protective and antigen-specific effect of heat-killed Mycobacterium vaccae in a murine model of allergic pulmonary inflammation.
AU Zuany-Amorim Claudia; Manlius Corinne; Trifilieff Alexandre; Brunet Laura R; Rook Graham; Bowen Gareth; Pay Graham; Walker Christoph
CS Novartis Horsham Research Center, Novartis Pharmaceutical Ltd., Horsham, United Kingdom.. claudia.zuany_amorim_fromond@pharma.novartis.com
SO Journal of immunology (Baltimore, Md. : 1950), (2002 Aug 1) 169 (3) 1492-9.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200208
ED Entered STN: 20020727
Last Updated on STN: 20020814
Entered Medline: 20020813
AB This report examines the effect of heat-killed Mycobacterium vaccae in a mouse model of allergic pulmonary inflammation. The s.c. administration of M. vaccae 3 wk before the immunization significantly reduced Ag-induced airway hyperreactivity and the increase in the numbers of eosinophils observed in the bronchoalveolar lavage fluid, blood, and bone marrow, even though no detectable changes in either cytokine (IL-4, IL-13, IL-5, and IFN-gamma) or total IgE levels were observed. Furthermore, transfer of splenocytes from OVA-immunized and M. vaccae-treated mice into recipient, OVA-immunized mice significantly reduced the allergen-induced eosinophilia by an IFN-gamma-independent mechanism, clearly indicating that the mechanism by which M. vaccae induces its inhibitory effect is not due to a redirection from a predominantly **Th2** to a **Th1** -dominated immune response. The protective effect of M. vaccae on the allergen-induced eosinophilia lasted for at least 12 wk after its administration, and the treatment was also effective in presensitized mice. Moreover, the allergen specificity of the inhibitory effect could be demonstrated using a double-immunization protocol, where M. vaccae treatment before OVA immunization had no effect on the eosinophilic inflammation induced by later immunization and challenge with cockroach extract Ag. Taken together, these results clearly demonstrate that M. vaccae is effective in blocking allergic inflammation by a mechanism independent of IFN-gamma, induces long term and Ag-specific protection, and therefore has both prophylactic and therapeutic potential for the treatment of allergic diseases.

L8 ANSWER 51 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 32
AN 2003:34384 BIOSIS
DN PREV200300034384
TI Immunomodulatory effects of **CpG** oligodeoxynucleotides on established Th2 responses.
AU Kitagaki, Kunihiko; Jain, Vipul V.; Businga, Thomas R.; Hussain, Iftikhar; Kline, Joel N. [Reprint Author]
CS University of Iowa Hospitals and Clinics, 200 Newton Rd., C33GH, Iowa City, IA, 52242, USA
joel-kline@uiowa.edu
SO Clinical and Diagnostic Laboratory Immunology, (November 2002) Vol. 9, No. 6, pp. 1260-1269. print.
ISSN: 1071-412X (ISSN print).
DT Article
LA English
ED Entered STN: 8 Jan 2003

Last Updated on STN: 8 Jan 2003

AB **CpG** oligodeoxynucleotides (**CpG** ODNs) are known to induce type 1 T-helper-cell (Th1) responses. We have previously demonstrated that **CpG** ODNs administered during sensitization prevent Th2-mediated eosinophilic airway inflammation in vivo. We also reported that key Th1 cytokines, gamma interferon (IFN-gamma) and interleukin 12 (IL-12), are not necessary for this protection. Recent in vivo data suggest that **CpG** ODNs might also reverse established pulmonary eosinophilia. In order to clarify how **CpG** ODNs can inhibit established Th2 responses, we evaluated the cytokine production from splenocytes from antigen- and alum-immunized mice. Restimulation with antigen induced IL-5, which was clearly inhibited by coculture with **CpG** ODNs in a concentration-dependent manner. **CpG** ODNs also induced IFN-gamma, but in a concentration-independent manner. The inhibition of IL-5 production was not mediated through natural killer cells or via CD8+ T lymphocytes. Although IFN-gamma plays an important role in inhibition of antigen-induced IL-5 production by **CpG** ODNs, IFN-gamma was not the sole factor in IL-5 inhibition. **CpG** ODNs also induced IL-10, and this induction correlated well with IL-5 inhibition. Elimination of IL-10 reduced the anti-IL-5 effect of **CpG** ODNs, although incompletely. This may be because IFN-gamma, induced by **CpG** ODNs, is also inhibited by IL-10, serving as a homeostatic mechanism for the **Th1-Th2** balance. Overproduction of IFN-gamma was downregulated by **CpG** ODN-induced IL-10 via modulation of IL-12 production. These data suggest that **CpG** ODNs may inhibit established Th2 immune responses through IFN-gamma and IL-10 production, the latter serving to regulate excessive Th1 bias. These properties of **CpG** ODNs might be a useful feature in the development of immunotherapy adjuvants against allergic diseases such as asthma.

L8 ANSWER 52 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 33

AN 2003:86234 BIOSIS

DN PREV200300086234

TI Natural type I interferon-producing cells as a link between innate and adaptive immunity.

AU Kadowaki, Norimitsu [Reprint Author]; Liu, Yong-Jun

CS Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, 54 Shogoin Kawara-cho, Sakyo-ku, Kyoto, 606-8507, Japan kadowaki@kuhp.kyoto-u.ac.jp

SO Human Immunology, (December 2002) Vol. 63, No. 12, pp. 1126-1132. print. CODEN: HUIMDQ. ISSN: 0198-8859.

DT Article

LA English

ED Entered STN: 6 Feb 2003
Last Updated on STN: 6 Feb 2003

AB Type I interferons (IFNs) are promptly produced upon invasion of pathogens, and activate a broad range of effector cells in the innate and adaptive immune system. Lin-CD4+CD11c- plasmacytoid dendritic cell precursors (plasmacytoid pre-DCs) produce enormous amounts of type I IFNs in response to viruses and **CpG** DNA, thus corresponding to the previously described but not fully defined natural type I IFN-producing cells (IPCs). Plasmacytoid pre-DCs strongly express toll-like receptor (TLR) 7 and TLR9, in contrast to monocytes, which mainly express TLR1, 2, 4, 5, and 8, suggesting that these two DC precursors recognize different microbial molecules and that they may have developed through different evolutionary trails. Three different stimuli, **CpG** DNA plus CD40 ligand, interleukin-3 (IL-3), and herpes simplex virus, stimulate plasmacytoid pre-DCs to differentiate into DCs that induce distinct types of T helper cells, i.e., **Th1**, **Th2**, and IFN-gamma- and IL-10-producing T cells, respectively. The remarkable versatility of plasmacytoid pre-DCs distinguishes them from other cell types in the

immune system that have only limited functions, and suggests that these cells may play a key role in integrating the innate and adaptive aspects of various immune responses.

L8 ANSWER 53 OF 159 MEDLINE on STN
AN 2002427392 MEDLINE
DN PubMed ID: 12184918
TI B cells express Ly-6C in a **Th1** but not **Th2** cytokine environment.
AU Schlueter Annette J; Krieg Arthur M; De Vries Peter; Li Xiang
CS Department of Pathology, University of Iowa College of Medicine, Iowa City, IA 52242-1181, USA.. schluetera@uihc.uiowa.edu
SO Journal of interferon & cytokine research : official journal of the International Society for Interferon and Cytokine Research, (2002 Jul) 22 (7) 799-806.
Journal code: 9507088. ISSN: 1079-9907.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200302
ED Entered STN: 20020820
Last Updated on STN: 20030212
Entered Medline: 20030211
AB Interferon-alpha (IFN-alpha) is the primary regulator of transient Ly-6C expression on T cells. B cells, which do not express Ly-6C in the resting state, have been reported to express Ly-6C following exposure to proinflammatory stimuli. This study examined the factors controlling Ly-6C expression on B cells and the kinetics of Ly-6C expression in the presence of these factors. In vivo studies demonstrated that proinflammatory (Th1) cytokines transiently upregulate B cell Ly-6C expression. In vitro studies identified Th1 cytokines, particularly IFN-alpha and IFN-gamma, as the principal cytokines responsible for this induction. Polyclonal B cell activators (anti-IgM and recombinant CD40 ligand trimer) showed minimal ability to independently induce Ly-6C expression on B cells but did enhance the ability of IFNs to induce expression. Th2 cytokine environments did not result in B cell Ly-6C expression, and interleukin-4 (IL-4) actually antagonized the IFN-driven induction of Ly-6C. Ly6.1 strains of mice consistently demonstrated a greater ability to express Ly-6C on B cells than did Ly-6.2 strains. Together, these studies demonstrate the ability of **Th1** but not **Th2** cytokine environments to transiently induce the expression of Ly-6C on B cells and provide additional evidence for differences in the regulation of Ly-6C expression in Ly6.1 and Ly6.2 strains.

L8 ANSWER 54 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 34
AN 2002:168588 BIOSIS
DN PREV200200168588
TI Improved immunogenicity and efficacy of the recombinant 19-kilodalton merozoite surface protein 1 by the addition of oligodeoxynucleotide and aluminum hydroxide gel in a murine malaria vaccine model.
AU Near, Karen A. [Reprint author]; Stowers, Anthony W.; Jankovic, Dragana; Kaslow, David C.
CS Opportunistic Infections Research Branch, Therapeutics Research Program, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 6700 B Rockledge, Rm. 5226, Bethesda, MD, 20892-7624, USA
knear@niaid.nih.gov
SO Infection and Immunity, (February, 2002) Vol. 70, No. 2, pp. 692-701. print.
CODEN: INFIBR. ISSN: 0019-9567.
DT Article

LA English
ED Entered STN: 5 Mar 2002
Last Updated on STN: 5 Mar 2002
AB Vaccination of mice with yeast-secreted Plasmodium yoelii-derived 19-kilodalton merozoite surface protein 1 (yMSP119) has been shown to afford protection from challenge with a lethal strain of P. yoelii. Sterile immunity can be achieved when MSP119 is emulsified in Freund adjuvant but not when it is adsorbed to aluminum hydroxide gel (alum). Because complete Freund adjuvant is not an acceptable adjuvant for use in humans, alternative adjuvants must be identified for formulating MSP119 as a vaccine for use in humans. To determine whether oligodeoxynucleotides with **CpG** motifs (ODN), reported to be a powerful new class of adjuvants, could enhance the immunogenicity of yMSP119, C57BL/6 mice were vaccinated either with yMSP119 formulated with Freund adjuvant, with alum, or with ODN plus alum and challenged intravenously with P. yoelii 17XL asexual blood-stage parasites. Adsorption of immunogen and adjuvant to alum was optimized by adjusting buffer (phosphate versus acetate) and pH. We found that the adjuvant combination of ODN plus alum with yMSP119, injected intraperitoneally (i.p.), increased immunoglobulin G (IgG) yMSP119-specific antibody production 12-fold over Freund adjuvant given i.p., 3-fold over Freund adjuvant given subcutaneously (s.c.), 300-fold over alum given i.p., and 48-fold over alum given s.c. The predominant antibody isotype in the group receiving alum-ODN-yMSP119 was IgG1. Increased antibody levels correlated to protection from a challenge with P. yoelii 17XL. Supernatant cytokine levels of gamma interferon in yMSP119-stimulated splenocytes were dramatically elevated in the alum-ODN-yMSP119 group. Interleukin-10 (IL-10) levels were also elevated; however, no IL-5 was detected. The cytokine profile, as well as the predominant IgG1 antibody isotype, suggests the protective immune response was a mixed **Th1/Th2** response.

L8 ANSWER 55 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 35
AN 2003:44723 BIOSIS
DN PREV200300044723
TI **CpG** DNA induced IL-12 p40 gene activation is independent of STAT1 activation or production of interferon consensus sequence binding protein.
AU Bradford, Mary; Schroeder, Arin J.; Morse, Herbert C. III; Vogel, Stefanie N.; Cowdery, John S. [Reprint Author]
CS Department of Internal Medicine, University of Iowa, 601 Highway 6 West, 6W34 VA Medical Center, Iowa City, IA, 52246, USA
john-cowdery@uiowa.edu
SO Journal of Biomedical Science, (November-December 2002) Vol. 9, No. 6 Part 2, pp. 688-696. print.
ISSN: 1021-7770.
DT Article
LA English
ED Entered STN: 15 Jan 2003
Last Updated on STN: 15 Jan 2003
AB The host immune system responds to **CpG** motifs in bacterial DNA by rapidly producing proinflammatory cytokines. The host response to **CpG** DNA resembles, in many ways, the response to bacterial lipopolysaccharide (LPS). While both agents can induce a powerful inflammatory response, **CpG** DNA promotes **Th1** and suppresses **Th2** immunity. The regulation of macrophage IL-12 p40 secretion in response to stimulation with LPS and interferon-gamma (IFN-gamma) is dependent on the action of a nuclear transacting factor, interferon consensus sequence binding protein (ICSBP), a STAT1-dependent gene product. We found that **CpG** DNA induced IL-12 p40 secretion by macrophages from mice with either disrupted STAT1 or ICSBP genes. Additionally, **CpG** DNA did not induce translocation of transcription factors that bind to the gamma-activated sequence in the

ICSBP gene nor did **CpG** DNA induce ICSBP transcription. **CpG** DNA, which activates macrophages by the TLR9 pathway, is a strong inducer of IL-12 p40, yet does so independently of IFN-gamma, STAT1 or ICSBP. Thus, **CpG** DNA-induced IL-12 p40 secretion is mediated by one or more signaling elements distinct from those induced by either LPS or IFN-gamma.

L8 ANSWER 56 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:780765 CAPLUS
DN 138:88429
TI Bacterial motif DNA as an adjuvant for the breakdown of immune self-tolerance to pyruvate dehydrogenase complex
AU Jones, David E. J.; Palmer, Jeremy M.; Burt, Alastair D.; Walker, Claire; Robe, Amanda J.; Kirby, John A.
CS Centre for Liver Research, University of Newcastle, Newcastle-upon-Tyne, UK
SO Hepatology (Philadelphia, PA, United States) (2002), 36(3), 679-686 CODEN: HPTLD9; ISSN: 0270-9139
PB W. B. Saunders Co.
DT Journal
LA English
AB Bacterial DNA containing unmethylated **CpG** dinucleotide motifs is immunostimulatory to mammals, skewing CD4+ T-cell responses toward the Th1 phenotype. Autoreactive T-cell responses seen in primary biliary cirrhosis (PBC) are typically of the Th1 phenotype, raising the possibility that bacterial DNA might play a role in the generation of pathol. autoimmunity. We therefore studied the effects of **CpG** motif-containing oligodeoxynucleotides (ODN) on responses to pyruvate dehydrogenase complex (PDC, the autoantigen in PBC) in a murine model. Sensitization of SJL/J mice with non-self-PDC has been shown to result in induction of autoreactive T-cell responses to PDC sharing characteristics with those seen in patients with PBC. Administration of **CpG** ODN to SJL/J mice at the time of sensitization with PDC resulted in a significant skewing of splenic T-cell response to self-PDC, with significant augmentation of the Th1 cytokine response (interleukin [IL] 2 and interferon [IFN] gamma) and reduction of the Th2 response (IL-4 and IL-10). In fact, **CpG** ODN seemed to be more effective at biasing the response phenotype and as effective at inducing liver histol. change as complete Freund's adjuvant (CFA), the standard adjuvant used for induction of Th1 responses in murine autoimmune and infectious immunity models. In conclusion, our findings raise the possibility that bacteria play a role in the development of autoimmunity (in PBC at least) through the potential of their DNA to shift the T-cell responses toward the phenotype associated with autoimmune damage. Moreover, this study suggests caution in the therapeutic use of **CpG** ODN as vaccine adjuvants.
RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 57 OF 159 MEDLINE on STN DUPLICATE 36
AN 2002426361 MEDLINE
DN PubMed ID: 12183170
TI Recent advances in mucosal vaccines and adjuvants.
AU Eriksson Kristina; Holmgren Jan
CS Department of Medical Microbiology and Immunology and Goteborg University Vaccine Research Institute (GUVAX), Goteborg University, Guldhedsgatan 10A, 413 46 Goteborg, Sweden.. kristina.eriksson@microbio.gu.se
SO Current opinion in immunology, (2002 Oct) 14 (5) 666-72. Ref: 37 Journal code: 8900118. ISSN: 0952-7915.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English

FS Priority Journals
EM 200302
ED Entered STN: 20020817
Last Updated on STN: 20030207
Entered Medline: 20030206
AB Mucosal vaccines may be used both to prevent mucosal infections through the activation of antimicrobial immunity and to treat systemic inflammatory diseases through the induction of antigen-specific mucosal tolerance. New, efficient mucosal adjuvants for human use have been designed based on, amongst others, bacterial toxins and their derivatives, **CpG**-containing DNA, and different cytokines and chemokines, with the aim of improving the induction of mucosal **Th1** and **Th2** responses. Mucosal delivery systems, in particular virus-like particles, have been shown to enhance the binding, uptake and half-life of the antigens, as well as target the vaccine to mucosal surfaces. DNA vaccines are currently being developed for administration at mucosal surfaces. However, there have also been failures, such as the withdrawal of an oral vaccine against rotavirus diarrhea and a nasal vaccine against influenza, because of their potential side effects.

L8 ANSWER 58 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:431884 CAPLUS
DN 137:45825
TI Th2 lineage commitment and efficient IL-4 production involves extended demethylation of the IL-4 gene
AU Lee, Dong U.; Agarwal, Suneet; Rao, Anjana
CS Department of Pathology, Harvard Medical School and The Center for Blood Research, Boston, MA, 02115, USA
SO Immunity (2002), 16(5), 649-660
CODEN: IUNIEH; ISSN: 1074-7613
PB Cell Press
DT Journal
LA English
AB The relation of **CpG** methylation to gene silencing is well established, but the contribution of DNA demethylation to gene expression during cell differentiation remains unclear. We show that the IL-4 locus undergoes a complex series of methylation and demethylation steps during T helper cell differentiation. The 5' region of the IL-4 locus is hypermethylated in naive T cells and becomes specifically demethylated in Th2 cells, whereas a highly conserved DNase I-hypersensitive region at the 3' end shows the converse behavior, being hypomethylated in naive T cells and becoming methylated during Th1 differentiation. 5' Demethylation is not required for chromatin remodeling or primary transcription of the IL-4 gene but is strongly associated with efficient, high-level induction of IL-4 transcripts by differentiated Th2 cells.
RE.CNT 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 59 OF 159 MEDLINE on STN DUPLICATE 37
AN 2002426358 MEDLINE
DN PubMed ID: 12183167
TI Allergy immunotherapy and inhibition of Th2 immune responses: a sufficient strategy?.
AU Lewis David B
CS Division of Immunology and Transplantation Biology, Department of Pediatrics, CCSR Building, Room 2115b, 269 Campus Drive, Stanford University School of Medicine, Stanford, California 94305-5164, USA.. dblewis@stanford.edu
SO Current opinion in immunology, (2002 Oct) 14 (5) 644-51. Ref: 80
Journal code: 8900118. ISSN: 0952-7915.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200302
ED Entered STN: 20020817
Last Updated on STN: 20030207
Entered Medline: 20030206
AB Th2 immune responses mediated by the secretion of IL-4, IL-5 and IL-13 are key in the pathogenesis of atopic disorders, including allergen-induced asthma, rhinoconjunctivitis and anaphylaxis. Although such responses are downregulated to some degree by conventional specific immunotherapy, this approach is only partially effective and has a substantial risk of adverse effects. Many strategies for immunotherapeutic prophylaxis and for treatment of atopic diseases have been devised on the basis of mouse allergy and autoimmune models, including the downregulation of Th2 responses by the induction of regulatory T cell activity, **Th2** to **Th1** immune deviation, **Th1** crossregulation of **Th2** immune responses, anergy and immunosuppressive cytokines. The blockade of events that are not allergen-specific, such as T cell costimulation and downstream events dependent on IgE, cytokines and chemokines, has also been pursued. With the exception of monoclonal antibody therapy for the blockade of IgE effector function, the application of most of these strategies to humans is at an early stage. Whether the inhibition of **Th2** responses without concurrent downregulation of **Th1** responses will be sufficient for allergic immunotherapy, particularly for atopic dermatitis and asthma, is an important but unresolved issue.

L8 ANSWER 60 OF 159 MEDLINE on STN DUPLICATE 38
AN 2002385740 MEDLINE
DN PubMed ID: 12133504
TI **CpG**-ODN is a potential candidate adjuvant for human vaccines.
AU Xu Honglin; Wang Shifeng; Guo Fei; Lu Roujian; Ruan Li
CS Department of Viral Genetics and Immunology, Institute of Virology, Chinese Academy of Preventive Medicine, Beijing 100052, China.
SO Zhonghua yi xue za zhi, (2002 Apr 25) 82 (8) 553-6.
Journal code: 7511141. ISSN: 0376-2491.
CY China
DT Journal; Article; (JOURNAL ARTICLE)
LA Chinese
FS Priority Journals
EM 200209
ED Entered STN: 20020723
Last Updated on STN: 20020926
Entered Medline: 20020925
AB OBJECTIVE: To evaluate the adjuvanticity of **CpG**-ODN for human vaccines in animal models. METHODS: To find suitable animal models, the human **CpG**-ODN were examined for their in vitro immunostimulatory activities for murine and Rhesus monkey immune cells. Then by using recombinant HBsAg as a model antigen, the adjuvanticity of human **CpG**-ODN was evaluated in the animal models. RESULTS: Rhesus monkey B cells responded well to all the human **CpG**-ODN, similarly as that of human B cells. In contrast, only the human **CpG**-ODN with the **CpG** motif 5'GTCGTT 3' (CpG2006 etc) could induce murine splenocytes to secret IgM and IFN-gamma, while those with the **CpG** motif 5'GTCGTC 3' (CpGT7 etc) had less or no effects. The results suggested that Rhesus monkeys and mice could be used as animal models to evaluate the in vivo activities of different human **CpG**-ODN. Immunized with HBsAg combined with various human **CpG**-ODN, the mice elicited a stronger Th1 humoral immunity. Consistent with the in vitro findings, **CpG**-ODN with the **CpG** motif 5'GTCGTT 3' were more potent than those with the **CpG** motif 5'GTCGTC 3'. But of note, all the sequences had the same ability for modulation of **Th1/Th2** immune

response, with the ratio of IgG2a/IgG1 around 1. However, human **CpG**-ODN had less adjuvanticity for HBsAg in Rhesus monkeys; only CpGT7 increased the antibody titers by 2 times, while CpG2006 had no effect. CONCLUSION: The preliminary results derived from animal models showed that **CpG**-ODN was a potential candidate Th1 adjuvant for human vaccines.

L8 ANSWER 61 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:733600 CAPLUS
DN 136:133163
TI DNA immunomodulation of asthma
AU Kline, Joel N.; Ballas, Zuhair K.
CS University of Iowa College of Medicine, Iowa City, IA, USA
SO Clinical Allergy and Immunology (2002), 16(Inflammatory Mechanisms in Allergic Diseases), 551-564
CODEN: CALMEH; ISSN: 1075-7910
PB Marcel Dekker, Inc.
DT Journal; General Review
LA English
AB A review discusses the different approaches for DNA-based modulation of asthma. These approaches are classified into several categories, i.e. control of bronchial reactivity, direct introduction of specific cytokines, global induction of **Th1**, and suppression of **Th2** cytokines.
RE.CNT 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 62 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 39
AN 2002:241950 BIOSIS
DN PREV200200241950
TI Amb a 1-linked **CpG** oligodeoxynucleotides reverse established airway hyperresponsiveness in a murine model of asthma.
AU Santeliz, Joanna V.; Van Nest, Gary; Traquina, Paula; Larsen, Elizabeth; Wills-Karp, Marsha [Reprint author]
CS Division of Immunobiology, Children's Hospital Medical Center, 3333 Burnet Ave., Cincinnati, OH, 45229-3039, USA
SO Journal of Allergy and Clinical Immunology, (March, 2002) Vol. 109, No. 3, pp. 455-462. print.
CODEN: JACIBY. ISSN: 0091-6749.
DT Article
LA English
ED Entered STN: 17 Apr 2002
Last Updated on STN: 17 Apr 2002
AB Background: Recently, it has been demonstrated that immunostimulatory DNA sequences (**ISS**) containing **CpG** motifs prevent the development of allergic airway responses in murine models of disease. However, few studies have addressed the issue of whether these agents will reverse established TH2-driven allergic airway responses. Objective: The aim of this study was to determine whether intradermal delivery of an immunogenic protein of ragweed pollen linked to an immunostimulatory DNA sequence could reverse an established allergic response in the mouse lung. Methods: Mice sensitized and challenged with ragweed pollen extract were treated intradermally twice at 1-week intervals with an **ISS** chemically linked to Amb a 1 (Amb a 1-**ISS**). One week after the Amb a 1-**ISS** treatment, mice were rechallenged intratracheally with ragweed extract, and airway responses were assessed. Results: Amb a 1-**ISS** treatment of ragweed-sensitized and ragweed-challenged mice significantly reversed allergen-induced airway hyperresponsiveness and suppressed the total number of eosinophils in bronchoalveolar lavage fluid. The inhibitory effect of Amb a 1-**ISS** was associated with a marked increase in IFN-gamma levels by Amb a 1-stimulated splenocytes and a shift in the antibody profile from a **TH2**-directed IgG1

response to a **TH1**-directed IgG2a response. Interestingly, the inhibitory effect of Amb a 1-**ISS** on allergen-driven airway hyperresponsiveness was independent of suppression of TH2 cytokine production. Conclusion: These results demonstrate that intradermal delivery of allergen-specific DNA conjugates can reverse established allergic responses in the murine lung, supporting their potential use in the treatment of human asthma.

L8 ANSWER 63 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2003:328411 BIOSIS
DN PREV200300328411
TI Toll-like receptors in the induction of adaptive immunity.
AU Barton, Gregory [Reprint Author]
CS Yale Univ. and Howard Hughes Med. Inst., New Haven, CT, USA
SO Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (2002) Vol. 42, pp. 446. print.
Meeting Info.: 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy. San Diego, CA, USA. September 27-30, 2002. American Society for Microbiology.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 16 Jul 2003
Last Updated on STN: 16 Jul 2003
AB Members of the Toll-like receptor (TLR) family have evolved to recognize a number of conserved microbial components (PAMPs), such as LPS, peptidoglycan, unmethylated **CpG** DNA, and flagellin. Recognition of these PAMPs leads to activation of the innate immune system, maturation of dendritic cells (DC), production of inflammatory cytokines, and, subsequently, activation of the adaptive immune system. It is becoming clear that signaling through different TLRs can result in different outcomes, although the mechanisms responsible for these different responses are not yet known. We have examined the role of TLRs in DC maturation and the initiation of adaptive immune responses. We have used mice deficient for individual TLRs or the common TLR adaptor, MyD88, to demonstrate the role of TLRs in the initiation of **Th1** versus **Th2** responses and the production of specific antibody isotypes.

L8 ANSWER 64 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 40
AN 2002:384633 BIOSIS
DN PREV200200384633
TI How instruction and feedback can select the appropriate T helper response.
AU Bergmann, Claudia [Reprint author]; van Hemmen, J. Leo; Segel, Lee A.
CS Department of Virology, Erasmus University Rotterdam, NL-3015, Rotterdam, Netherlands
bergmann@viro.fgg.eur.nl
SO Bulletin of Mathematical Biology, (May, 2002) Vol. 64, No. 3, pp. 425-446. print.
CODEN: BMTBAP. ISSN: 0092-8240.
DT Article
LA English
ED Entered STN: 10 Jul 2002
Last Updated on STN: 10 Jul 2002
AB The decision of the immune system to trigger immune responses that are, respectively, induced by **Th1** or **Th2** effectors is a critical one, because it profoundly influences disease outcome. We have recently constructed a mathematical model of **Th1-Th2** -pathogen interactions that shows that the major decisional events can often be successfully determined by the intrinsic behaviour of the T helper system itself. For certain dangerous types of pathogens, however, which replicate rapidly or have developed strategies to evade the immune response, additional stimuli may be necessary. As a possible mechanism

for the decision-making process innate immune recognition has been proposed. Here we present an enlarged version of our model, which incorporates signals created from the innate immune system after pathogen recognition. The model analysis suggests that there is fault-tolerance of the T helper system to incorrect Th1 signals. In the presence of incorrect Th1 stimuli an initial Th1 response is shifted to the correct Th2-dominated response owing to the intrinsic T helper dynamics. By contrast, according to our model there is no fault-tolerance for incorrect Th2 signals. In fact, if timing is unimportant then Th2 signals are superfluous since the intrinsic T helper dynamics provide an automatic switch to **Th2** if **Th1** effectors fail to control the pathogen. Th2 signals may, however, be required to accelerate the onset of the Th2 response. Additionally, we discuss the role of feedback where successful pathogen destruction leads to up-regulation of activation of the effective T helper type. As one possibility we examine the role of **CpG** motifs as indicators for successful pathogen destruction. Differences between instructive and feedback mechanisms are high-lighted.

L8 ANSWER 65 OF 159 MEDLINE on STN DUPLICATE 41
AN 2002702650 MEDLINE
DN PubMed ID: 12463765
TI **CpG** DNA in the prevention and treatment of infections.
AU Dalpke Alexander; Zimmermann Stefan; Heeg Klaus
CS Institute of Medical Microbiology and Hygiene, Philipps University, Marburg, Germany.
SO BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy, (2002) 16 (6) 419-31. Ref: 161
Journal code: 9705305. ISSN: 1173-8804.
CY New Zealand
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200307
ED Entered STN: 20021217
Last Updated on STN: 20030703
Entered Medline: 20030702
AB Microbial infection is sensed by Toll-like receptors (TLRs) on innate immune cells. Among the ten so far defined TLRs, TLR9 and its ligand are peculiar. TLR9 recognises bacterial DNA characterised by the abundance of unmethylated **CpG** dinucleotides, which distinguish bacterial DNA (**CpG** DNA) from mammalian DNA. Moreover, TLR9 shows a restricted cellular and subcellular pattern of expression. In contrast to other TLR agonists, **CpG** DNA is superior in activation of dendritic dells and induction of costimulatory cytokines such as interleukin (IL)-12 and IL-18. This qualifies **CpG** DNA as a Th1-promoting adjuvant. During infection, recognition of **CpG** DNA of intracellular pathogens skews and fine-tunes the ongoing immune response and induces long-lasting Th1 milieus. Thus, **CpG** DNA might play an important role in driving the immune system to a **Th1** profile, preventing undesired **Th2** milieus that might favour induction of allergic responses. Since **CpG** DNA can be synthesised with high purity and sequence fidelity, synthetic **CpG** DNA will become an important agent for Th1 instruction and be an effective adjuvant during vaccination.

L8 ANSWER 66 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:720101 CAPLUS
DN 140:216061
TI An experimental study of prevention of **CpG** DNA on production of a murine asthmatic model
AU Jin, Meiling; Cai, Yingyun; Yuan, Zhenghong; Zheng, Lingjie; Zhang, Wei

CS Zhongshan Hospital, Fudan University, Shanghai, 200032, Peop. Rep. China
SO Fudan Xuebao, Yixueban (2002), 29(5), 376-378
CODEN: FXYUAO
PB Fudan Xuebao, Yixueban Bianji Weiyuanhui
DT Journal
LA Chinese
AB The prevention by **CpG** DNA of murine allergic asthma was investigated. Eighteen female BALB/c mice were divided into 3 groups. Mice in group **CpG** and group ovalbumin (OVA) were sensitized s.c. with OVA/alum and challenged with OVA; group NS were injected and challenged with normal saline (NS). Group **CpG** was injected **CpG** DNA 100 μg/100 μL i.p. prior to sensitization. Blood samples, bronchoalveolar lavage fluid (BALF), lung tissues and spleen cells were collected one day after the challenge. Serum OVA-specific IgE, IgG1, IgG2a were measured by ELISA; total cell nos. and classification of BALF were counted; IFN-γ produced by OVA-stimulated spleen cells was determined by ELISA. Pathol. examination showed that in group **CpG** airway inflammation and eosinophil infiltration in airway and lung parenchyma were inhibited as compared with group OVA. In group **CpG** total cell nos., eosinophilia of BALF and serum levels of IgE and IgG1 were decreased, while the serum level of IgG2a and the level of IFN-γ in spleen cell supernatants were increased as compared with group OVA. It is indicated that **CpG** DNA could prevent murine asthma.

L8 ANSWER 67 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2002:353819 BIOSIS
DN PREV200200353819
TI **CpG** DNA induces IL-12 p40 gene activation independent of STAT1 activation or production of interferon consensus sequence binding protein (ICSBP).
AU Cowdery, John S. [Reprint author]; Schroeder, Arin J. [Reprint author]; Morse, Herbert C.; Vogel, Stefanie N.; Bradford, Mary A. [Reprint author]
CS IA and Dept. of IM, College of Medicine, DVAMC Iowa City, UI, Hwy 6, Iowa City, IA, 52246, USA
SO FASEB Journal, (March 20, 2002) Vol. 16, No. 4, pp. A322. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology. New Orleans, Louisiana, USA. April 20-24, 2002.
CODEN: FAJOEC. ISSN: 0892-6638.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 26 Jun 2002
Last Updated on STN: 26 Jun 2002
AB The host immune system responds to **CpG** motifs in bacterial DNA by rapidly producing proinflammatory cytokines. The host response to **CpG** DNA resembles, the response to bacterial lipopolysaccharide (LPS). While both agents induce a powerful inflammatory response, **CpG** DNA promotes **Th1** and suppress **Th2** immunity. Additionally, **CpG** DNA is a more potent inducer of IL-12 secretion. Work by others has established the importance of an interferon-gamma (IFN-gamma) induced transcription factor, interferon consensus sequence binding protein (ICSBP) in the regulation of the IL-12 p40 response. Since **CpG** DNA alone is a potent inducer of IL-12 production, we tested the hypothesis that **CpG** DNA possesses IFN-gamma-like properties. We examined the ability of **CpG** DNA to activate the STAT pathway or to activate ICSBP which is controlled by STAT1. **CpG** DNA does not induce translocation of STAT1, nor induce transcription of the ICSBP gene. Additionally, macrophages from mice defective with respect to STAT1 or ICSBP secrete p40 in response to **CpG** DNA. These findings illustrate that the IFN-gamma-like properties of **CpG** DNA are independent of either STAT1 or ICSBP, and that IL-12 p40 expression can occur independent of ICSBP.

L8 ANSWER 68 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:838712 CAPLUS
DN 138:135279
TI Modulation of allergic conjunctivitis by immunostimulatory DNA sequence oligonucleotides
AU Keane-Myers, Andrea; Chan, Chi-Chao
CS Laboratory of Allergic Disease, NIAID/NIH, Bethesda, MD, USA
SO Microbial DNA and Host Immunity (2002), 315-325. Editor(s): Raz, Eyal. Publisher: Humana Press Inc., Totowa, N. J.
CODEN: 69DFSH; ISBN: 1-58829-022-0
DT Conference; General Review
LA English
AB A review which describes the therapeutic potentials of immunostimulatory sequence oligodeoxynucleotide (**ISS**-ODN) to treat allergic eye disease, particularly, allergic conjunctivitis. **ISS** provides a danger/alarm-like signal required for the vital T helper 1 (Th1) immune response. The significant increase in asthma and allergies could be a side effect of progress in the area of infection control. The administration of **ISS**-ODN can be used to shift **Th1**/**Th2** balance in exptl. and models of allergy.
RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 69 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:838711 CAPLUS
DN 138:151694
TI **CpG** oligodeoxynucleotides in asthma
AU Kitagaki, Kunihiko; Kline, Joel N.
CS Division of Pulmonary Medicine, University of Iowa Health Center, Iowa City, IA, USA
SO Microbial DNA and Host Immunity (2002), 301-314. Editor(s): Raz, Eyal. Publisher: Humana Press Inc., Totowa, N. J.
CODEN: 69DFSH; ISBN: 1-58829-022-0
DT Conference; General Review
LA English
AB A review evaluates the effects of **CpG**-oligodeoxynucleotide on asthma using an allergen-induced model of asthma in mice. **CpG** -ODN are strong T helper 1 (Th1) inducers, and **Th1** cytokines could inhibit **Th2** immune responses. Th1 cytokines are not required for **CpG**-ODN to exert protective effects against allergen-induced airway eosinophilia, and airway hyperactivity because **CpG**-ODN are effective even in the absence of both IFN-γ and IL-12.
RE.CNT 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 70 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:838709 CAPLUS
DN 138:135278
TI Immunostimulatory DNA for allergic asthma
AU Ikeda, Reid K.; Takabayashi, Kenji; Broide, David
CS Department of Medicine, University of California at San Diego, La Jolla, CA, USA
SO Microbial DNA and Host Immunity (2002), 289-299. Editor(s): Raz, Eyal. Publisher: Humana Press Inc., Totowa, N. J.
CODEN: 69DFSH; ISBN: 1-58829-022-0
DT Conference; General Review
LA English
AB A review discusses mechanisms of action and potential efficacy of DNA-based approach, with emphasis on the immunostimulatory sequence (**ISS**)-protein allergen conjugate therapy, in the treatment of asthma. Exon-coding DNA vaccines are designed to inhibit T helper 2 (Th2) immune response to specific DNA encoded allergens. **ISS** therapy

redirects the host immune response from **Th2** to a **Th1** response. **ISS**-allergen protein conjugate therapy improves the efficacy of unconjuagated **ISS** therapy by targeting **ISS** and the protein allergen to the same antigen-presenting cell.
RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 71 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2002:353634 BIOSIS
DN PREV200200353634
TI Distinct **CpG** ODN with high IFN-alpha induction drive monocytes towards an activated phenotype which promotes the development of effector memory CD8 T cells.
AU Sarris, Anja [Reprint author]; Krug, Anne [Reprint author]; Selinger, Sibylle [Reprint author]; Rothenfusser, Simon [Reprint author]; Bock, Carmen [Reprint author]; Jahrsdoerfer, Bernd [Reprint author]; Endres, Stefan [Reprint author]; Hartmann, Gunther [Reprint author]
CS Department of Internal Medicine, Division of Clinical Pharmacology, Ludwig-Maximilians-University Munich, Ziemssenstrasse 1, Munich, Munich, 80336, Germany
SO FASEB Journal, (March 20, 2002) Vol. 16, No. 4, pp. A288. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology. New Orleans, Louisiana, USA. April 20-24, 2002.
CODEN: FAJOEC. ISSN: 0892-6638.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 26 Jun 2002
Last Updated on STN: 26 Jun 2002
AB Recently we identified a new type of **CpG** ODN which is characterized by the induction of high amounts of type I IFN in plasmacytoid dendritic cells resulting in strong NK cell activation. In the present study we examined the effects of this type of **CpG** ODN on human primary monocytes. In PBMC stimulated with **CpG** ODN and GMCSF, monocytes rapidly increased in size and granularity and within three days developed a phenotype characterized by partial downregulation of CD14, increased surface expression of costimulatory (CD80, CD86, CD40) and antigen-presenting molecules (MHC I, MHC II) and expression of IL-15 but not IL-12. These cells were unable to upregulate CD83, IL-12 and CCR7 upon different maturation stimuli. In T cell assays, this monocyte-derived cell type, but not immature monocyte-derived dendritic cells generated in the presence of GMCSF and IL-4, selectively increased the frequency of allogeneic CCR7- and CD45RA- CD8 effector memory T cells. Consistent with the lack of IL-12, **Th1** versus **Th2** bias of CD4 T cells was not affected. The generation of this **CpG** ODN-induced monocyte-derived cell type was dependent on the presence of IFN-alpha, but the addition of recombinant IFN-alpha was not sufficient for its development. We propose a model in which this so far unappreciated cell type via IL-15 selectively recruits effector memory CD8 T cells and displays an important function to limit viral infection at the site of pathogen entrance.

L8 ANSWER 72 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:100596 CAPLUS
DN 138:203238
TI **CpG** oligodeoxynucleotides and their potential role in the immunotherapy of allergic diseases
AU Krieg, A. M.
CS Department of Internal Medicine, University of Iowa, Iowa City, IA, 52242, USA
SO New Trends in Allergy V, [International Symposium], 5th, Davos, Switzerland, Sept. 15-17, 2000 (2002), Meeting Date 2000, 273-278.
Editor(s): Ring, Johannes; Behrendt, Heidrun. Publisher: Springer-Verlag,

Berlin, Germany.
CODEN: 69DOXF; ISBN: 3-540-43082-2
DT Conference; General Review
LA English
AB A review about the effect of **CpG** DNA on **Th1** and **Th2** immune responses and as a aid in immunotherapy of allergy.
RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 73 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 42
AN 2003:101977 BIOSIS
DN PREV200300101977
TI Enhancement of immune responses by co-delivery of a **CpG** oligodeoxynucleotide and tetanus toxoid in biodegradable nanospheres.
AU Diwan, Manish; Tafaghodi, Mohsen; Samuel, John [Reprint Author]
CS Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, 3118 Dentistry/Pharmacy Center, Edmonton, AB, T6G 2N8, Canada
jsamuel@pharmacy.ualberta.ca
SO Journal of Controlled Release, (13 December 2002) Vol. 85, No. 1-3, pp. 247-262. print.
ISSN: 0168-3659 (ISSN print).
DT Article
LA English
ED Entered STN: 19 Feb 2003
Last Updated on STN: 19 Feb 2003
AB Synthetic oligodeoxynucleotides (ODN) consisting of unmethylated bacterial DNA sequences with **CpG** motifs are potent immunological adjuvants. Immunostimulatory **CpG** sequences are species-specific. Optimal **CpG** sequences specific for humans, rodents, livestock, and companion animals have been reported. Nearly all of these reports describe the use of soluble forms of **CpG** ODN and antigens. We investigated the co-delivery of **CpG** ODN and antigens in biodegradable nanospheres as an alternative approach for immunization using tetanus toxoid (TT) as the model antigen and ODN 1826 as the model **CpG** sequence. TT and **CpG** ODN were co-encapsulated in poly(D,L-lactic-co-glycolic acid) nanospheres. Separate groups of C57BL/6 mice were subcutaneously immunized twice with TT and **CpG** ODN in nanospheres (test group), TT alone in nanospheres, TT alone in nanospheres mixed with **CpG** ODN in solution, TT and **CpG** ODN both in solution (reference group), TT alone in solution, and alum adsorbed TT. T cells isolated from the test group showed strong antigen-specific T cell proliferation ex vivo (stimulation index=45). This was significantly ($P<0.0001$) higher than that observed for T cells isolated from the reference group. The T cell proliferation of the test group was associated with higher levels of interferon gamma secretion (IFN-gamma 2694.7+-41.1 pg/ml) than that of the reference group (814.7+-50.2 pg/ml). Interleukin 4 (IL-4) secretion, if any, was below the detection limit (<13 pg/ml) in all the groups. Anti-sera obtained from the test group also showed very high total IgG titers (end point titers, 2 560 000) that were 16 times higher than the reference group. Similarly, differences of 8-fold for IgG1 and IgG3, and 5-fold for IgG2b titers were observed. Noticeably, the antibody response induced in the alum-TT group was far less (total IgG, end point titers 160 000) than that obtained in the TT-**CpG** ODN nanospheres group. Overall, the results show that co-delivery of **CpG** and TT resulted in induction of both T helper type 1 and type 2 (**Th1** and **Th2**) immune responses with a bias towards Th1 type. These results suggest that the co-delivery of **CpG** ODN adjuvants and antigens in nanospheres is a more efficient approach for immunization than the use of **CpG** ODN and TT in solution.

L8 ANSWER 74 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

DUPLICATE 43
AN 2003:104228 BIOSIS
DN PREV200300104228
TI **CpG** motifs as possible adjuvants for the treatment of allergic diseases.
AU Bohle, Barbara [Reprint Author]
CS Department of Pathophysiology, Division of Immunopathology, University of Vienna, Waehringer Guertel 18-20, AKH-3Q, A-1090, Vienna, Austria barbara.bohle@akh-wien.ac.at
SO International Archives of Allergy and Immunology, (November 2002) Vol. 129, No. 3, pp. 198-203. print.
CODEN: IAAIEG. ISSN: 1018-2438.
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 19 Feb 2003
Last Updated on STN: 19 Feb 2003
AB DNA containing unmethylated **CpG** motifs and synthetic oligodeoxynucleotides derived thereof (**CpG** ODN) have intensively been investigated for their immunostimulatory properties in the recent past. **CpG** ODN were shown to induce strong Th1 immune responses in mammals. The downregulation of the antigen-driven Th2 response of type I allergies represents one important therapeutic goal of specific immunotherapy (SIT). Hence, **CpG** ODN represent promising substances which support the modification of the pathogenic **Th2** immune profile toward a **Th1** profile when used as adjuvants for SIT. This article discusses how the use of **CpG** ODN in immunotherapeutics could improve the treatment of type I allergy.

L8 ANSWER 75 OF 159 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 44
AN 2002124079 EMBASE
TI Parenteral and mucosal prime-boost immunization strategies in mice with hepatitis B surface antigen and **CpG** DNA.
AU McCluskie M.J.; Weeratna R.D.; Payette P.J.; Davis H.L.
CS M.J. McCluskie, Coley Pharmaceutical Group, 725 Parkdale Avenue, Ottawa, Ont. K1Y 4E9, Canada. mmccluskie@coleypharma.com
SO FEMS Immunology and Medical Microbiology, (18 Feb 2002) 32/3 (179-185). Refs: 30
ISSN: 0928-8244 CODEN: FIMIEV
PUI S 0928-8244(01)00305-4
CY Netherlands
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB Synthetic oligodeoxynucleotides (ODN) containing immunostimulatory **CpG** motifs (**CpG** ODN) are potent adjuvants to protein antigens administered by parenteral or mucosal routes to BALB/c mice. To date, there have been no studies using combined parenteral/mucosal approaches with **CpG** DNA as adjuvant. In this study we evaluated different parenteral prime-mucosal boost and mucosal prime-parenteral boost strategies using hepatitis B surface antigen (HBsAg) alone or with different adjuvants: aluminum hydroxide (alum), cholera toxin (CT), **CpG** ODN. In addition, since **CpG** ODN has previously been shown to act synergistically with other adjuvants after parenteral or mucosal delivery, we also evaluated adjuvant combinations: alum+ **CpG** ODN and CT+**CpG** ODN. The effects of adjuvant and administration strategy on systemic and mucosal humoral responses were measured, as well as cell-mediated immune responses (cytotoxic T lymphocyte activity). These results were compared to parenteral only or

mucosal only strategies. Our findings demonstrate that parenteral immunization can prime for mucosal responses even when different lymph nodes were being targeted. HBsAg-specific immune responses (IgG in plasma, cytotoxic T lymphocytes) induced by parenteral prime could all be significantly enhanced by mucosal boosting and despite the fact that intramuscular immunization alone could not induce mucosal IgA, it could prime for a subsequent mucosal boost. In addition, the presence of adjuvant at time of boosting could influence the nature of subsequent immune responses (**Th1** vs. **Th2**). Mice primed intranasally could have their systemic immune responses boosted with a parenteral administration and it was also possible to enhance mucosal responses induced by intranasal prime with an intramuscular boost.

L8 ANSWER 76 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 45
AN 2002:447850 BIOSIS
DN PREV200200447850
TI Treatment of established asthma in a murine model using **CpG** oligodeoxynucleotides.
AU Kline, Joel N. [Reprint author]; Kitagaki, Kunihiko; Businga, Thomas R.; Jain, Vipul V.
CS Univ. of Iowa Hospitals and Clinics, 200 Newton Rd., C33GH, Iowa City, IA, 52242, USA
joel-kline@uiowa.edu
SO American Journal of Physiology, (July, 2002) Vol. 283, No. 1 Part 1, pp. L170-L179. print.
CODEN: AJPHAP. ISSN: 0002-9513.
DT Article
LA English
ED Entered STN: 21 Aug 2002
Last Updated on STN: 21 Aug 2002
AB Allergen immunotherapy is an effective but underutilized treatment for atopic asthma. We have previously demonstrated that **CpG** oligodeoxynucleotides (**CpG** ODN) can prevent the development of a murine model of asthma. In the current study, we evaluated the role of **CpG** ODN in the treatment of established eosinophilic airway inflammation and bronchial hyperreactivity in a murine model of asthma. In this model, mice with established ovalbumin (OVA)-induced airway disease were given a course of immunotherapy (using low doses of OVA) in the presence or absence of **CpG** ODN. All mice then were rechallenged with experimental allergen. Untreated mice developed marked airway eosinophilia and bronchial hyperresponsiveness, which were significantly reduced by treatment with OVA and **CpG**. **CpG** ODN leads to induction of antigen-induced Th1 cytokine responses; successful therapy was associated with induction of the chemokines interferon-gamma-inducible protein-10 and RANTES and suppression of eotaxin. Unlike previous studies, these data demonstrate that the combination of **CpG** ODN and allergen can effectively reverse established atopic eosinophilic airway disease, at least partially through redirecting a **Th2** to a **Th1** response.

L8 ANSWER 77 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:382461 CAPLUS
DN 138:66463
TI Effects of **CpG**-ODN on the expression of **Th1**/**Th2** cytokines in a murine model of asthma
AU Zhang, Zuyi; Yang, Yuan; Zhang, Jianping
CS Department of Respiratory Diseases, Zhongda Hospital, Southeast University, Nanjing, 210009, Peop. Rep. China
SO Jiangsu Yiyao (2002), 28(3), 164-166
CODEN: CIYADX; ISSN: 0253-3685

PB Jiangsu Yiyao Bianjibu
DT Journal
LA Chinese
AB The effects of phosphorothioate oligonucleotides containing **CpG** motifs (**CpG**-ODN) on **Th1/Th2** related cytokines immunomodulation and airway eosinophil inhibition in a murine model of atopic asthma were studied. The serum levels of **Th1** cytokine IFN γ and **Th2** cytokine IL-4 were measured by ELISA on 24 h after the first and the last challenge of ovalbumin (OVA), and eosinophil in peripheral blood and BALF was counted. 24 H after the last challenge, the IFN γ level in serum and BALF of **CpG** -ODN group was higher than that in dexamethasone (DXM) group ($P < 0.001$). 24 H after the first and last challenges, the IL-4 level in serum and BALF of **CpG**-ODN group was lower than that in asthma group, and there were no significant difference between **CpG**-ODN group and DXM group ($P > 0.05$). **CpG**-ODN enhanced Th1 cytokine IFNγ expression and down-regulated Th2 cytokine IL-4 expression, and may play an important role of immunomodulation on **Th1/Th2**.

L8 ANSWER 78 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:838693 CAPLUS
DN 138:151687
TI Immunostimulatory DNA prepriming for the induction of **Th1** and prevention of **Th2** biased immune responses
AU Kobayashi, Hiroko; Martin-Orozco, Elena; Takabayashi, Kenji; Horner, Anthony A.
CS Department of Internal Medicine II, Fukushima Medical University School of Medicine, Fukushima, Japan
SO Microbial DNA and Host Immunity (2002), 163-174. Editor(s): Raz, Eyal. Publisher: Humana Press Inc., Totowa, N. J.
CODEN: 69DFSH; ISBN: 1-58829-022-0
DT Conference; General Review
LA English
AB A review presenting data suggesting that in gene vaccinated animals, **ISS**-ODN within the plasmid DNA backbone generate a type 1 cytokine milieu and induce the expression of costimulatory mols. on APCs and B cells. A novel paradigm for Th1 biased immunization that was called **ISS**-ODN prepriming is also presented.
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 79 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:838692 CAPLUS
DN 138:151686
TI The Th1 adjuvant effect of immunostimulatory (**ISS**) DNA sequences
AU Corr, Maripat; Tang, Chih Min
CS Division of Rheumatology, Allergy and Immunology, and The Sam and Rose Stein Institute for Research on Aging, Department of Medicine, University of California at San Diego, La Jolla, CA, USA
SO Microbial DNA and Host Immunity (2002), 153-162. Editor(s): Raz, Eyal. Publisher: Humana Press Inc., Totowa, N. J.
CODEN: 69DFSH; ISBN: 1-58829-022-0
DT Conference; General Review
LA English
AB A review discusses the **TH1** and **TH2** effects of DNA immunization. **ISS**, owing to a wide range of stimulatory effects, has been found to be a potent adjuvant in inducing Th1 immune responses. Direct stimulation of macrophages and dendritic cells causes the release of IL-12 and other Th1 promoting factors. The use of **ISS** as adjuvants has therapeutic implications for the development of vaccines to combat infections or neoplasms.
RE.CNT 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 80 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 46
AN 2003:19221 BIOSIS
DN PREV200300019221
TI **CpG**-containing oligodeoxynucleotides, in combination with conventional adjuvants, enhance the magnitude and change the bias of the immune responses to a herpesvirus glycoprotein.
AU Ioannou, X. P.; Gomis, S. M.; Karvonen, B.; Hecker, R.; Babiuk, L. A.; van Drunen Littel-van den Hurk, S. [Reprint Author]
CS Veterinary Infectious Disease Organization, 120 Veterinary Road, Saskatoon, Sask., S7N 5E3, Canada
vandenhurk@sask.usask.ca
SO Vaccine, (22 November 2002) Vol. 21, No. 1-2, pp. 127-137. print.
ISSN: 0264-410X (ISSN print).
DT Article
LA English
ED Entered STN: 1 Jan 2003
Last Updated on STN: 1 Jan 2003
AB Vaccine adjuvants must have the capacity to increase protective immune responses with minimal side effects. Conventional adjuvants not only cause undesirable tissue site reactions, but often induce T-helper type 2 (Th2)-biased responses which may be undesirable in certain disease scenarios. Oligodeoxynucleotides containing unmethylated **CpG** dinucleotides (**CpG** ODN) are novel adjuvants known to promote Th1-type immune responses. In this study, we compared various mineral oil, metabolizable oil and non-oil adjuvants alone and in combination with **CpG** ODN for their ability to augment immune responses to a truncated secreted form of bovine herpesvirus (BHV) glycoprotein D (tgD). All adjuvants tested induced Th2-biased immune responses characterized by a predominance of serum IgG1 as well as interleukin-4 (IL-4) production by in vitro stimulated splenocytes. The inclusion of **CpG** ODN in these formulations not only increased immune responses, but more importantly enhanced serum IgG2a levels and production of interferon-gamma (IFN-gamma) by splenocytes, indicating a more balanced or Th1-type response. The use of a mineral oil-based adjuvant at reduced doses in combination with **CpG** ODN attenuated the tissue damage while not compromising the magnitude of the immune response in both mice and sheep. In addition, reduced amounts of mineral oil combined with **CpG** ODN induced a more balanced **Th1/Th2** immune response than the mineral oil used alone. Our results clearly demonstrate that **CpG** ODN can be used to enhance magnitude and balance of an immune response while reducing the amount of mineral oil and hence undesirable side effects of vaccine adjuvants.

L8 ANSWER 81 OF 159 MEDLINE on STN DUPLICATE 47
AN 2002227435 MEDLINE
DN PubMed ID: 11964753
TI DNA therapy for asthma.
AU Kline Joel N
CS Department of Medicine, University of Iowa, 200 Newton Road, Iowa City, IA 52242, USA.. joel-kline@uiowa.edu
SO Current opinion in allergy and clinical immunology, (2002 Feb) 2 (1) 69-73. Ref: 13
Journal code: 100936359. ISSN: 1528-4050.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200208
ED Entered STN: 20020420

Last Updated on STN: 20020823
Entered Medline: 20020822

AB Asthma therapy, like other therapies, has been moving towards a molecular basis for several years. This year, there have been several preclinical studies published which utilize attributes or facets of DNA to address asthma therapeutics. These include antisense oligonucleotides (against the nuclear transcription factor GATA-3 and the mast cell chemotactic agent, stem cell factor), gene transfer (of interleukin-18, both by plasmid and viral vectors), and **CpG** oligodeoxynucleotides (which suppress **Th2** and stimulate **Th1** responses). No clinical experience has yet been reported for any of these areas of research in asthma, but clinical trials are ongoing utilizing **CpG** oligonucleotides.

L8 ANSWER 82 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 48
AN 2003:47965 BIOSIS
DN PREV200300047965
TI Therapeutic effect of **CpG** motifs on the development of chronic graft-versus-host disease in mice.
AU Senuma, Akiko; Hagiwara, Eri; Nagahama, Kiyotaka; Okuda, Kenji; Nakamura, Mitsuyuki; Fukumoto, Natsuko; Shirai, Akira; Tani, Kenji; Ishigatsubo, Yoshiaki [Reprint Author]
CS First Department of Internal Medicine, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, 236-0004, Japan
ishigats@med.yokohama-cu.ac.jp
SO Cytokine, (7 October 2002) Vol. 20, No. 1, pp. 23-29. print.
ISSN: 1043-4666 (ISSN print).
DT Article
LA English
ED Entered STN: 15 Jan 2003
Last Updated on STN: 15 Jan 2003
AB Transferring DBA/2 spleen cells into (C57BL/10XDBA/2) F1 (referred to as BDF1) mice induces a chronic graft-versus-host disease (GVHD), characterized by the production of Th2 cytokines, hypergammaglobulinemia, and immune complex-mediated glomerulonephritis that resembles systemic lupus erythematosus. DNA motif consisting of an unmethylated **CpG** dinucleotide flanked by two 5' purines and two 3' pyrimidines (**CpG** ODN) induces Th1 cytokine production in mice. This study examines the effect of administering **CpG** ODN to mice undergoing chronic GVHD, based on the premise that altering **Th1/Th2** activity might beneficially impact on disease progression. GVHD BDF1 mice injected with DBA/2 spleen cells were treated with weekly intraperitoneal injection of 50 mug **CpG** ODN. This treatment significantly suppressed the production of IgG anti-DNA autoantibody and reduced the development of glomerulonephritis. Serum IgG2a titers were higher in the **CpG** ODN than in non-**CpG** control group, whereas IgG1 titers were unchanged. As predicted, IFN-gamma levels were significantly higher in the **CpG** ODN-treated group, while IL-4 levels were lower, resulting in a shift in the **Th1/Th2** cytokine ratio. Results suggest that **CpG** ODN administration may be of therapeutic benefit in chronic GVHD.

L8 ANSWER 83 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 49
AN 2002:175122 BIOSIS
DN PREV200200175122
TI Is **Th1** the solution for **Th2** in asthma?.
AU Tournoy, K. G. [Reprint author]; Kips, J. C.; Pauwels, R. A.
CS Department of Respiratory Diseases, Ghent University Hospital, De Pintelaan 185, 7 K12 I.E., 9000, Ghent, Belgium
kurt.tournoy@rug.ac.be
SO Clinical and Experimental Allergy, (January, 2002) Vol. 32, No. 1, pp.

17-29. print.
ISSN: 0954-7894.
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 6 Mar 2002
Last Updated on STN: 6 Mar 2002

L8 ANSWER 84 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:233179 CAPLUS
DN 139:285330
TI The promise of **CpG** DNA in the treatment of asthma
AU Jain, Vipul V.; Kline, Joel N.
CS Department of Internal Medicine, Division of Pulmonary, Critical Care and Occupational Medicine, University of Iowa, Iowa City, IA, 52242, USA
SO Recent Research Developments in Respiratory & Critical Care Medicine (2002), 2(Pt. 1), 7-18
CODEN: RRDRBZ
PB Research Signpost
DT Journal; General Review
LA English
AB A review. Atopy is an immune disorder of hypersensitivity to innocuous environmental antigens (allergens), and a major cause of asthma world-wide. The prevalence, morbidity, mortality, and cost of asthma were on the rise in the past few decades and are a growing health concern, especially in the industrialized countries. In this review the authors discuss the epidemiol. of enhanced prevalence of asthma, and the **Th1**/**Th2** paradigm of inflammation in asthma. The authors discuss data that illustrate the potential of **CpG** DNA in the treatment of asthma, and therefore suggest that **CpG** DNA may provide a novel immunomodulatory agent in the therapy of asthma.
RE.CNT 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 85 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:299320 CAPLUS
DN 136:308127
TI Immunostimulatory DNA and the host-pathogen relationship
AU Van Uden, John Henry, IV
CS Univ. of California, San Diego, CA, USA
SO (2001) 137 pp. Avail.: UMI, Order No. DA3013707
From: Diss. Abstr. Int., B 2001, 62(5), 2248
DT Dissertation
LA English
AB Unavailable

L8 ANSWER 86 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 50
AN 2002-130570 [17] WPIDS
DNC C2002-040090
TI New immunostimulatory compositions comprising RNA/DNA hybrid oligonucleotides, useful for enhancing an immune response or inducing cytokines, particularly for treating diseases, e.g. cancer, allergy or HIV infection.
DC B04 D16
IN FLORA, M; KLINMAN, D M; MOND, J J
PA (BIOS-N) BIOSYNEXUS INC; (FLOR-I) FLORA M; (KLIN-I) KLINMAN D M; (MOND-I) MOND J J
CYC 97
PI WO 2001093902 A2 20011213 (200217)* EN 68
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2001075294 A 20011217 (200225)

EP 1292331 A2 20030319 (200322) EN

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR

US 2004052763 A1 20040318 (200421)

ADT WO 2001093902 A2 WO 2001-US18276 20010607; AU 2001075294 A AU 2001-75294 20010607; EP 1292331 A2 EP 2001-941989 20010607, WO 2001-US18276 20010607; US 2004052763 A1 Provisional US 2000-209797P 20000607, US 2001-874991 20010607

FDT AU 2001075294 A Based on WO 2001093902; EP 1292331 A2 Based on WO 2001093902

PRAI US 2000-209797P 20000607; US 2001-874991 20010607

AB WO 200193902 A UPAB: 20020313

NOVELTY - An immunostimulatory composition, which comprises at least one oligonucleotide comprising both an RNA region and a DNA region, is new. At least one terminus of the oligonucleotide comprises RNA.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an adjuvant comprising the immunostimulatory composition;

(2) vaccines (I) comprising:

(a) at least one oligonucleotide comprising both an RNA region and a DNA region, where at least one terminus of the oligonucleotide comprises RNA, where the oligonucleotide is associated with a physiological carrier or delivery system;

(b) at least one oligonucleotide comprising both an RNA region and a DNA region, where at least one terminus of the oligonucleotide comprises RNA, and at least one target antigen;

(3) a method of stimulating innate immunity comprising administering at least one oligonucleotide comprising both an RNA region and a DNA region, where at least one terminus of the oligonucleotide comprises RNA, and where the oligonucleotide is associated with a physiological carrier or delivery system;

(4) a method of stimulating global immunity comprising administering at least one oligonucleotide comprising both an RNA region and a DNA region, where at least one terminus of the oligonucleotide comprises RNA, and where the oligonucleotide is associated with a physiological carrier or delivery system;

(5) methods of stimulating a cellular immune response or a humoral immune response comprising administering the vaccine of (Ib); and

(6) a method of making a vaccine comprising associating:

(a) at least one oligonucleotide comprising both an RNA region and a DNA region, where at least one terminus of the oligonucleotide comprises RNA; and

(b) a physiological carrier or delivery system.

ACTIVITY - Immunostimulant; antiallergic; cytostatic; antimicrobial; immunosuppressive; anti-HIV; protozoacide; virucide; hepatotropic; antiinflammatory; antibacterial.

MECHANISM OF ACTION - Gene therapy; cytokine stimulator; vaccine. The stimulation of cytokines interleukin-6 (IL-6) and interferon gamma (IFN-gamma) in human peripheral lymphocytes cultured from four healthy volunteer subjects, designated S1 through S4, was assayed using standard methods. Oligonucleotides DDD and RDR were added to the media of cultured cells to final concentrations of 0.3, 3, or 30 micro g/ml. 24 hours after oligonucleotide addition, **Th1** and **Th2**-type cytokine levels in the media were determined by enzyme linked immunoabsorbant assay (ELISA). The hybrid DNA/RNA oligonucleotides stimulated the production of cytokines implicated in eliciting both **Th1** (IFN- gamma) and **Th2** T (IL-6) type responses in human peripheral lymphocytes. At the highest concentrations tested, for example, the hybrid RDR molecule

was 3-fold more effective at inducing IFN- gamma and 5-fold more effective at stimulating the release of IL-6.

USE - The composition is useful for enhancing an immune response or inducing cytokines. The compositions comprising the oligonucleotides are useful as vaccine adjuvants and in treating diseases, e.g. pathogenic infection, (non-)malignant tumors (e.g. cancers of the brain, lung, ovary, breast, prostate or colon, or carcinomas and sarcomas), autoimmune disease or allergy (e.g. allergic rhinitis, hay fever or food allergies), lyme disease, hepatitis, HIV or malaria. The composition is also useful for treating, preventing or ameliorating the symptoms resulting from exposure to a bio-warfare agent, e.g. Ebola, Anthrax or Listeria.

Dwg.0/0

L8 ANSWER 87 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:440338 BIOSIS
DN PREV200100440338
TI **Immunostimulatory nucleic acid** molecules.
AU Krieg, Arthur M. [Inventor]; Kline, Joel [Inventor, Reprint author]; Klinman, Dennis [Inventor]; Steinberg, Alfred D. [Inventor]
CS Iowa City, IA, USA
ASSIGNEE: University of Iowa Research Foundation; Coley Pharmaceutical Group, Inc., Wellesley, MA, USA; The United States of America as represented by the Department of Health and Human Services
PI US 6207646 March 27, 2001
SO Official Gazette of the United States Patent and Trademark Office Patents, (Mar. 27, 2001) Vol. 1244, No. 4. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 19 Sep 2001
Last Updated on STN: 22 Feb 2002
AB Nucleic acids containing unmethylated **CpG** dinucleotides and therapeutic utilities based on their ability to stimulate an immune response and to redirect a **Th2** response to a **Th1** response in a subject are disclosed.

L8 ANSWER 88 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-582389 [65] WPIDS
CR 2002-049002 [06]; 2003-312719 [30]
DNC C2001-172732
TI Immunomodulatory polynucleotide/microcarrier complexes comprise an immunostimulatory sequence containing polynucleotide linked to a nonbiodegradable microcarrier.
DC B04 D16
IN TUCK, S; VAN NEST, G; NEST, G V; DINA, D; FEARON, K L
PA (DYNA-N) DYNAVAX TECHNOLOGIES CORP; (NEST-I) NEST G V; (TUCK-I) TUCK S; (DINA-I) DINA D; (FEAR-I) FEARON K L; (VNES-I) VAN NEST G
CYC 96
PI WO 2001068143 A2 20010920 (200165)* EN 61
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001045628 A 20010924 (200208)
US 2002055477 A1 20020509 (200235)
EP 1261377 A2 20021204 (200280) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
US 2003059773 A1 20030327 (200325)
JP 2004502645 W 20040129 (200413) 118
ADT WO 2001068143 A2 WO 2001-US7843 20010312; AU 2001045628 A AU 2001-45628

20010312; US 2002055477 A1 Provisional US 2000-188557P 20000310, US 2001-802376 20010309; EP 1261377 A2 EP 2001-918568 20010312, WO 2001-US7843 20010312; US 2003059773 A1 Provisional US 2000-188557P 20000310, CIP of US 2001-802376 20010309, US 2001-927884 20010810; JP 2004502645 W JP 2001-566706 20010312, WO 2001-US7843 20010312

FDT AU 2001045628 A Based on WO 2001068143; EP 1261377 A2 Based on WO 2001068143; JP 2004502645 W Based on WO 2001068143

PRAI US 2001-802376 20010309; US 2000-188557P 20000310; US 2001-927884 20010810

AB WO 200168143 A UPAB: 20040511

NOVELTY - An immunomodulatory polynucleotide/microcarrier complex, comprising a an immunostimulatory sequence (**ISS**) linked to a nonbiodegradable microcarrier provided that if the microcarrier is gold, latex or magnetic then the linkage is not biotin/avidin, is new.

DETAILED DESCRIPTION - An immunomodulatory polynucleotide/microcarrier complex, comprising a an immunostimulatory sequence (**ISS**) linked to a nonbiodegradable microcarrier provided that if the microcarrier is gold, latex or magnetic then the linkage is not biotin/avidin, is new. (**ISS**) is 5'C, G-3'.

INDEPENDENT CLAIMS are also included for the following:

(1) modulating an immune response, interferon-gamma, or interferon-alpha, and reducing levels of immunoglobulin (Ig)E, comprising administration of the novel complex; and

(2) a kit comprising the novel complex in a container.

ACTIVITY - Immunomodulatory.

MECHANISM OF ACTION - None given.

USE - The complex is useful for modulating an immune response (especially stimulating a **Th1**-type response or suppressing a **Th2**-type response), increasing interferon-gamma (especially in a patient suffering from idiopathic pulmonary fibrosis), increasing interferon-alpha (especially in patients suffering from viral infection) and reducing levels of IgE (claimed).

Dwg.0/0

L8 ANSWER 89 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2001-483193 [52] WPIDS

CR 2000-514893 [44]

DNC C2001-144884

TI Autovaccination against a pathogen present in the body by intermittent administration of a drug therapy, useful for helping infected individuals achieve immune control of antiviral infections e.g. HIV infection and hepatitis B infection.

DC B04 D16

IN LISZIEWICZ, J; LORI, F; VARGA, G S; XU, J

PA (REGE-N) RES INST GENETIC & HUMAN THERAPY

CYC 84

PI WO 2001054652 A2 20010802 (200152)* EN 92

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW

AU 2001032970 A 20010807 (200174)

ADT WO 2001054652 A2 WO 2001-US2458 20010126; AU 2001032970 A AU 2001-32970 20010126

FDT AU 2001032970 A Based on WO 2001054652

PRAI US 2000-493769 20000128

AB WO 200154652 A UPAB: 20010914

NOVELTY - A method (M1) of autovaccination against a pathogen present in the body using an optimum dose of the pathogen itself as an antigen to increase pathogen-specific immune responses where autovaccination is achieved by intermittent administration of a drug therapy, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a method (M2) of autovaccination against a pathogen present in the body using an optimum dose of the pathogen itself as an antigen to increase pathogen-specific immune responses where autovaccination is achieved by administration of a suboptimal drug therapy that does not completely inhibit the amount of the pathogen;

(2) a method (M3) of measuring an immune system's competence against a pathogen, comprising measuring changes in the pathogen-specific immune responses and pathogen load; and

(3) a diagnostic test for immune system competence against HIV, comprising testing the viral load in the plasma and the production in different cell types.

ACTIVITY - Antiviral.

The infection of rhesus macaques by Simian Immunodeficiency Virus (SI Vmac2Sl) was chosen as an animal model because of the similarities of SIV in macaques to HIV infection in humans. Mucosal inoculation of macaques with SlVmac25l reproducibly resulted in an infection characterized by peak plasma viremia within 2-3 weeks post infection, followed by a plateau which can persist for several months. Eventually, most animals progress toward an acquired immune deficiency syndrome, although, occasionally, a low percentage of infected animals manage to spontaneously control virus replication and exhibit very low levels of plasma viremia, similar to human long-term non-progressors.

A total of 29 rhesus macaques were infected via mucosal (intra-rectal) inoculation with SIVmac25l (5.12 x 103 TCID 50 in 3 ml). The combination of PMPA (20 mg/Kg once daily subcutaneously), ddl (10 mg/Kg once daily intravenously), and HU (Hydroxyurea, 15 mg/Kg once daily intravenously) was selected because preliminary experiments had shown that this combination can effectively suppress SIV viral load for long periods of time, similar to highly active antiretroviral therapy (HAART) in HIV infected humans. A group of five SIV infected and untreated animals served as controls. A group of six SIV infected animals received continuous antiretroviral therapy initiated 44 days post infection. The other 3 groups were treated intermittently for a total of 24 weeks. The groups treated intermittently were on the same schedule, 3 weeks on followed by 3 weeks off. In sum, Group 1 was untreated, Group 2 was treated with intermittent therapy, (HU + ddl + PMPA), Group 3 was treated with intermittent therapy that did not include hydroxyurea, (ddl + PMPA), Group 4 was treated with intermittent therapy for two drugs, ddl and PMPA, and continuous therapy for a third, hydroxyurea (ddl + PMPA, intermittent, HU continuous); Group 5 was treated continuous therapy (HU+ ddl + PMPA, continuous treatment).

The virology of this experiment demonstrates that both treatment schedules, continuous HAART and structured treatment interruptions (STI), decreased the viral load efficiently after introduction of therapy. Compared to the untreated control, the viral load in all cases was either undetectable or at a very low level during the treatments. The differences among the three STI therapies with respect to the maintenance of viral load were also insignificant during the treatment. This picture changed dramatically after permanent treatment interruption. The viral load of the animals rebounded in the group treated continuously with HAART (cont ddl+PMPA+HU) and one animal died one month after therapy interruption. No animals died in the untreated control group. This was not surprising, because it is known that after interruption of HAART, viral load rebounds to the pretreatment values or higher, even if it starts from a very low undetectable level. In contrast, the monkeys treated with STI controlled SIV replication at least 2 months after permanent interruption of therapy. In the group of STI(ddl+PMPA+HU) the results were dramatic: 6 of the 6 animals controlled SIV. In each of the two other groups of STI(ddl+PMPA) and STI(ddl+PMPA+cont HU) one animal was a non-responder (never responded to therapy, a finding not uncommon in the treatment of these animals, irrespective of the kind of treatment administered), one animal's viral

load rebounded, and 4 animals controlled SIV. These results demonstrate that continuos HAART cannot be interrupted because viral load rebounds rapidly and, more importantly, after therapy interruption, patients have a higher risk of dying than if they had remained untreated and Intermittent therapy (STI) can control viral replication after therapy discontinuation and Hydroxyurea is a useful but not essential component of HAART used for STI.

MECHANISM OF ACTION - Autovaccination by structured interruptions of drug treatment.

USE - The method is useful for help infected individuals achieve immune control of antiviral infections e.g. HIV infection and hepatitis B infection.

ADVANTAGE - The method increases the ability of the infected patients immune system to control a pathogen after treatment has stopped.

Dwg.0/15

L8 ANSWER 90 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-381378 [40] WPIDS
CR 1996-442364 [44]; 1997-363453 [33]; 1999-479189 [40]; 1999-610318 [52]; 2000-587309 [55]; 2000-611341 [58]; 2001-408258 [43]; 2002-739597 [80]; 2003-018765 [01]; 2003-786926 [74]; 2003-875632 [81]
DNC C2001-116829
TI Antigenic fragments useful for reducing anaphylactic risk and reducing the severity and/or number of allergic symptoms in individuals sensitive to antigens, have reduced ability to bind Immunoglobulin E.
DC B04 D16
IN BANNON, G A; BURKS, W A; CAPLAN, M J; SAMPSON, H; SOSIN, H
PA (MOUN) MOUNT SINAI SCHOOL MEDICINE NEW YORK; (PANA-N) PANACEA PHARM LLC; (UYAR-N) UNIV ARKANSAS
CYC 93
PI WO 2001040264 A2 20010607 (200140)* EN 100
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001019512 A 20010612 (200154)
ADT WO 2001040264 A2 WO 2000-US33124 20001206; AU 2001019512 A AU 2001-19512 20001206
FDT AU 2001019512 A Based on WO 2001040264
PRAI US 2000-235797P 20000927; US 1999-455294 19991206; US 2000-213765P 20000623
AB WO 200140264 A UPAB: 20031216

NOVELTY - A peptide (I) having a sequence of at least 6 amino acids identical to a portion of a sequence of an anaphylactic antigen (A), and having a reduced ability to bind immunoglobulin (Ig) E as compared with the intact (A), or having a sequence substantially identical to a portion of sequence of an antigen that includes at least one IgE binding site, where at least one IgE binding site of the peptide is altered, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a composition (C1) comprising a collection of peptide fragments of a protein antigen, the collection being characterized in that the fragment represent overlapping portions of the protein antigen's sequence, so that the entire protein antigen sequence is represented in the collection;

(2) a composition (C2) comprising (I) sufficient to reduce severity of one or more allergy symptoms in an individual sensitive to the antigen;

(3) a pharmaceutical composition (PC) comprising C1 sufficient to reduce severity of one or more allergy symptoms in an individual sensitive to the antigen; and

(4) a mouse that is sensitized to an anaphylactic antigen or a food

antigen.

ACTIVITY - Antiallergic.

MECHANISM OF ACTION - Vaccine.

Mice were sensitized intragastrically with freshly ground peanut (PN) on day 0 and boosted on day 7. To determine the optimum sensitizing dose, mice received 5 mg/mouse (low dose) or 25 mg/mouse (high dose) of PN together with 10 mu g/g of cholera toxin (CT). Three weeks after initial sensitization, mice were challenged intragastrically with crude extract 10 mg/mouse in 2 doses at 30-40 minutes intervals.

Sham sensitized mice were challenged in the same manner. Mice surviving the first challenge were re-challenged at weeks 5. Results showed systemic anaphylactic symptoms within 10-15 minutes of initial challenge, and the severity of anaphylaxis was evaluated at 30-40 minutes after second challenge. Further, severe reactions were observed in mice sensitized with low dose (5 mg/mouse + CT) of whole PN, than those sensitized with the high dose (25 mg/mouse + CT). Fatal or near fatal anaphylactic shock occurred in 12.5% of low dose sensitized mice but in none of the high dose sensitized mice. Sham sensitized mice and naive mice did not show any symptoms of anaphylaxis.

USE - (I) is useful for reducing risk or severity of allergic reaction to an antigen, by identifying an individual at risk of allergic reaction to an antigen by identifying an individual having a prior display of allergic symptoms when exposed to the antigen or a familial relationship with an individual who previously displayed allergic symptoms when exposed to the antigen, identifying an antigen-specific IgE present on one or more mast cells or basophils of the individual, in the individual's serum, contacting the individual with a peptide corresponding to a portion of the antigen, which is selected, formulated, and delivered so that binding of the peptide to antigen-specific IgE is reduced as compared with IgE binding of intact antigen (claimed).

The compositions are also useful for treating and preventing allergic reactions.

Dwg.0/15

L8 ANSWER 91 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-329209 [34] WPIDS
DNC C2001-101050
TI Populations of conjugate molecules comprising polynucleotide immunostimulatory sequences polynucleotides and antigens, useful for controlling immune responses.
DC B04 D16
IN TUCK, S; VAN NEST, G
PA (DYNA-N) DYNAVAX TECHNOLOGIES CORP
CYC 95
PI WO 2001035991 A2 20010525 (200134)* EN 93
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001016121 A 20010530 (200152)
EP 1229933 A2 20020814 (200261) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
JP 2003513680 W 20030415 (200328) 121
ADT WO 2001035991 A2 WO 2000-US31385 20001115; AU 2001016121 A AU 2001-16121 20001115; EP 1229933 A2 EP 2000-978688 20001115, WO 2000-US31385 20001115; JP 2003513680 W WO 2000-US31385 20001115, JP 2001-537981 20001115
FDT AU 2001016121 A Based on WO 2001035991; EP 1229933 A2 Based on WO 2001035991; JP 2003513680 W Based on WO 2001035991
PRAI US 2000-713136 20001114; US 1999-165467P 19991115
AB WO 200135991 A UPAB: 20011129

NOVELTY - Immunomodulatory populations ((I) and (II)) of conjugate molecules (CMs) comprising immunostimulatory sequences (ISSs) of polynucleotides and antigens. The extent of conjugation affects the immunological properties (e.g. the extent of antigen-specific antibody formation, including Th1-associated antibody formation) so the conjugates are used for altering the type and extent of immune response.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a population of conjugate molecules (CMs) (I), comprising an antigen and a polynucleotide comprising an immunostimulatory sequence (**ISS**) (the extent of the conjugation in the population means that the ratio of:

(i) concentration of **ISS**-antigen conjugate required for 50% inhibition of binding of antigen-specific antibody to antigen to;

(ii) concentration of antigen required for 50% inhibition of antigen-specific antibody to antigen is 3.5 to 6.0);

(2) a population of CMs (II), comprising an antigen and a polynucleotide comprising an **ISS** (the extent of the conjugation in the population means that the ratio of:

(i) concentration of **ISS**-antigen conjugate required for 40% histamine release from basophils from an antigen-sensitized individual to;

(ii) concentration of antigen required for 40% histamine release from basophils from an antigen-sensitized individual is more than 1000);

(3) a method (III) of modulating an immune response in an individual, comprising administering a composition comprising (I) to the individual to modulate the immune response; and

(4) a method (IV) of modulating an immune response in an individual, comprising administering a composition comprising (II) to the individual to modulate the immune response.

ACTIVITY - Immunomodulatory; immunosuppressive; antiallergic.

MECHANISM OF ACTION - Modulation of immune responses via the stimulation of Th1 lymphocytes and **Th1**-associated cytokines and suppression of **Th2** lymphocytes and cytokines.

Peripheral blood mononuclear cells (PBMCs) were prepared from blood of rag weed allergic human subjects. The cells were cultured at 2 multiply 106/ml with 5 micro g/ml of Amb a 1, AIC-M or AIC-H for 67 days (AIC-M and AIC-H were covalent conjugates of the ragweed allergen Amb a 1 and an **ISS**-containing polynucleotide sequence TGACTGTGAACGTTCGAGAT and comprised the same heterofunctional linker (production methods given in the specification)). Supernatants were harvested and the interferon (IFN)-gamma content of the supernatant was measured by enzyme linked immunosorbant assay (ELISA). Some cells were re-stimulated on day 6 with 2.5 micro g/ml phytohemagglutinin (PHA) and 10 ng/ml phorbol 12-myristate 13-acetate (PMA) for 24 hours, after which supernatant were harvested and the IL-4 and IL-5 content of the supernatants were measured by ELISA. Cytokine responses of the PBMCs from ragweed allergic subjects are given in the specification. Both AIC-H and AIC-M were able to stimulate a Th1-type cytokine response in cells from individuals allergic to ragweed. In contrast, Amb a 1 produced a Th2-type cytokine response from these cells, i.e. little IFN- gamma but higher levels of IL-4 and IL-5. This showed that AIC-M and AIC-H were effective in shifting the cytokine profile in PBMCs from allergic individuals to reflect a Th1-type response bias.

USE - The populations ((I) and (II)) of conjugate molecules may be used for modulating immune responses in individuals (via (III) and (IV)), e.g. for the treatment of an allergic condition.

ADVANTAGE - (I) And (II) may be used to modulate immune responses and therefore prevent potentially harmful reactions to antigens.

Dwg.0/16

L8 ANSWER 92 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-343486 [36] WPIDS
CR 2001-343824 [36]

DNN N2001-248746 DNC C2001-106345
TI Novel **CpG** receptor and nucleic acid molecule encoding the receptor, for modulating immune response and for identifying compounds of therapeutic use which bind and/or modulate the activity of the receptor.
DC B04 D16 S03
IN MACKICHAN, M L
PA (CHIR) CHIRON CORP
CYC 23
PI WO 2001032877 A2 20010510 (200136)* EN 41
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
W: CA JP US
EP 1226251 A2 20020731 (200257) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
JP 2003514219 W 20030415 (200328) 58
ADT WO 2001032877 A2 WO 2000-US41735 20001101; EP 1226251 A2 EP 2000-989738 20001101, WO 2000-US41735 20001101; JP 2003514219 W WO 2000-US41735 20001101, JP 2001-535559 20001101
FDT EP 1226251 A2 Based on WO 2001032877; JP 2003514219 W Based on WO 2001032877
PRAI US 1999-167389P 19991124; US 1999-163157P 19991102
AB WO 200132877 A UPAB: 20030501
NOVELTY - An isolated polypeptide (I) comprising an amino acid sequence encoding **CpG** receptor or its fragment, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) an isolated nucleic acid molecule (II) comprising a nucleotide sequence encoding (I), or its complement;
(2) an isolated nucleic acid molecule comprising a nucleotide sequence having at least 70% sequence identity with (II);
(3) a recombinant expression vector (III) comprising (II);
(4) host cells transformed with (III);
(5) producing (M1) (I);
(6) an isolated antibody (IV) which binds to an epitope on (I);
(7) a kit comprising (IV) and a control antibody; and
(8) modulating (M2) an immune response in a mammal by administering a compound which modulates and binds to **CpG** receptor.
ACTIVITY - Antitumor; antiinflammatory; antiallergic; antiarthritic. No supporting data is given.
MECHANISM OF ACTION - Modulator of **CpG** receptor activity.
USE - **CpG** receptor or cells expressing the receptor is useful for identifying a compound which binds to or modulates an activity of **CpG** receptor (claimed). Compounds that bind to or modulate **CpG** receptor are useful in e.g. vaccine adjuvants promoting cell-mediated immune responses, antibacterials, (e.g. protection from Listeria infection), tumor immunotherapy, allergy treatment, (e.g. suppressing IgE in human PBMC, shifting from **Th2** to **Th1**) and as anti-inflammatory agents (e.g. for use in cystic fibrosis, sepsis, heart disease, chlamydia, inflammatory bowel disease, arthritis and multiple sclerosis). **CpG** receptor or antibody to the receptor is useful for modulating an immune response in a mammal. (I) is useful for generating antibodies which are useful as a specific inhibitors of **CpG** receptor activity and in the isolation and purification of (I).
Dwg.0/4

L8 ANSWER 93 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-138610 [18] WPIDS
DNC C2002-042640
TI Inducing an antigen specific immune response useful in treating Th1-mediated inflammatory disorders, e.g., (non)-autoimmune diseases or cancer, comprises administering a Th2-**immunostimulatory nucleic acid** and an antigen.
DC B04 D16

IN DAVIS, H L; MCCLUSKIE, M J
PA (DAVI-I) DAVIS H L; (MCCL-I) MCCLUSKIE M J; (COLE-N) COLEY PHARM GROUP INC; (OTTA-N) OTTAWA HEALTH RES INST
CYC 95
PI US 2001044416 A1 20011122 (200218)* 50
WO 2001095935 A1 20011220 (200218) EN
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001031080 A 20011224 (200227)
EP 1311288 A1 20030521 (200334) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
ADT US 2001044416 A1 Provisional US 2000-177461P 20000120, US 2001-768012 20010122; WO 2001095935 A1 WO 2001-US2170 20010122; AU 2001031080 A AU 2001-31080 20010122; EP 1311288 A1 EP 2001-903236 20010122, WO 2001-US2170 20010122
FDT AU 2001031080 A Based on WO 2001095935; EP 1311288 A1 Based on WO 2001095935
PRAI US 2000-177461P 20000120; US 2001-768012 20010122
AB US2001044416 A UPAB: 20020319
NOVELTY - Methods using a Th2-**immunostimulatory nucleic acid** (I) to induce an antigen specific response by administration mucosally,dermally or parenterally with an antigen, to stimulate an antibody dependent cellular cytotoxic immune response, to treat non-autoimmune Th1 mediated disease and autoimmune disease, to prevent infectious diseases and cancer, are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a method (M1) for inducing an antigen specific response comprising administering an antigen and (I) to produce an antigen specific immune response when (I) is administered mucosally or dermally;

(2) a method (M2) of inducing an antigen specific response comprising administering an antigen and (I) to produce an antigen specific immune response when (I) is administered parenterally;

(3) treating (M3) a non-autoimmune Th1-mediated disease or an autoimmune disease by administering (I) mucosally or dermally;

(4) a method (M5) for treating or preventing an infectious disease in a subject by administering (I) mucosally, dermally, or parenterally, where the subject has not been exposed to a Th1 **immunostimulatory nucleic acid**;

(5) a method (M6) for treating or preventing a cancer in a subject by administering to a subject having a cancer or at risk of developing a cancer,(I) mucosally, dermally, or parenterally;

(6) a method (M7) for stimulating an antibody dependent cellular cytotoxic immune (ADCC) response in a subject by administering (I) and an antibody;

(7) a pharmaceutical composition (C1) comprising (I), that stimulates an Th2 immune response when administered mucosally or dermally, and an antigen;

(8) a pharmaceutical composition (C2) comprising (I) that stimulates an Th2 immune response when administered mucosally or dermally and an adjuvant;

(9) a pharmaceutical composition (C3) comprising (I) in an effective amount for inducing ADCC, a monoclonal antibody, and a pharmaceutically acceptable carrier; and

(10) a composition (C4) comprising (I) with a phosphodiester backbone, formulated in a delivery vehicle comprising bioadhesive polymers, enteric-coated capsules, microspheres, nanospheres, and polymer rings.

ACTIVITY - Immunostimulant; immunosuppressive; anti-inflammatory;

antiparasitic; cytostatic; antirheumatic; antiarthritic; dermatological; neuroprotective; virucide; hepatotropic; antipsoriatic; antidiabetic; antithyroid; gynecological; fungicide; antibacterial; dermatological; thyromimetic; nephrotropic; antianemic; hemostatic.

Mice were immunized by oral delivery with HBsAg (100 micro g) without adjuvant or in combination with **CpG** ODN (motif 1982, 100 micro g), non-**CpG** ODN (motif 1826, 100 or 500 micro g), or cholera toxin (CT, 10 micro g). Oral delivery of HBsAg without adjuvant resulted in none or only low anti-HBs IgG titers in the plasma of mice. In contrast, antibodies were detected where **CpG** ODN 1826, CT or non-**CpG** ODN 1982 were added. Compared to results obtained with CT, a classical mucosal adjuvant, HBsAG-specific IgG titers with 100 or 500 micro g non-**CpG** ODN were better or equally good. There was no significant difference between results obtained with an equivalent dose of non-**CpG** and **CpG** ODN. When antibody responses induced by the different formulations, the addition of non-**CpG** ODN augment both IgG1 and IgG2a but with a predominance of IgG1 as did CT. **CpG** ODN induced an equally mixed **Th1/Th2** response, which is much more **Th1**-biased than is obtained with HBsAg alone.

MECHANISM OF ACTION - None given.

USE - The methods are useful for treating and preventing disorders associated with a Th1 immune response, or for creating a Th2 environment for treating disorders that are sensitive to a **Th2** immune response. **Th1**-mediated disorders include autoimmune diseases (e.g., rheumatoid arthritis, Crohn's disease, systemic lupus erythematosus (SLE), autoimmune encephalomyelitis, myasthenia gravis, Hashimoto's thyroiditis, Goodpasture's syndrome, pemphigus, Grave's disease, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, scleroderma with anti-collagen antibodies, mixed connective tissue disease, polymyositis, pernicious anemia, idiopathic Addison's disease, autoimmune-associated infertility, glomerulonephritis, bullous pemphigoid, Sjogren's syndrome, insulin resistance, and autoimmune diabetes mellitus) and non-autoimmune diseases (e.g., psoriasis, Th1 inflammatory disorders, solid organ allograft rejection, symptoms associated with Hepatitis B infection, insulin-dependent diabetes mellitus, multiple sclerosis, silent thyroiditis, and unexplained recurrent abortion). The methods are also useful for treating or preventing parasitic infections, infectious diseases, cancer, for stimulating antibody dependent cellular cytotoxic immune response and for inducing an antigen specific response (all claimed).

Dwg.0/14

L8 ANSWER 94 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:693137 CAPLUS
DN 135:271874
TI Biodegradable immunomodulatory formulations and methods for use thereof
IN Van Nest, Gary; Tuck, Stephen
PA Dynavax Technologies Corporation, USA
SO PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001068144	A2	20010920	WO 2001-US7848	20010312
	WO 2001068144	A3	20020516		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,

VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	US 2003129251	A1	20030710	US 2001-802359	20010309
	EP 1261378	A2	20021204	EP 2001-918571	20010312
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003526682	T2	20030909	JP 2001-566707	20010312
PRAI	US 2000-188303P	P	20000310		
	US 2001-802359	A2	20010309		
	WO 2001-US7848	W	20010312		

AB The invention provides new compns. and methods for immunomodulation of individuals. Immunomodulation is accomplished by administration of immunomodulatory polynucleotide/microcarrier (IMP/MC) complexes. The IMP/MC complexes may be covalently or non-covalently bound, and feature a polynucleotide comprising at least one immunostimulatory sequence bound to a biodegradable microcarrier or nanocarrier.

L8 ANSWER 95 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 51
AN 2001:214669 BIOSIS
DN PREV200100214669
TI Adjuvantation of epidermal powder immunization.
AU Chen, Dexiang [Reprint author]; Erickson, Cherie A.; Endres, Ryan L.; Periwal, Sangeeta B.; Chu, Qili; Shu, Cassandra; Maa, Yuh-Fun; Payne, Lendon G.
CS PowderJect Vaccines Inc., 585 Science Drive, Madison, WI, 53711, USA
dexiang_chen@powderject.com
SO Vaccine, (6 April, 2001) Vol. 19, No. 20-22, pp. 2908-2917. print.
CODEN: VACCDE. ISSN: 0264-410X.
DT Article
LA English
ED Entered STN: 2 May 2001
Last Updated on STN: 18 Feb 2002
AB The skin is an immunologically active site and an attractive vaccination route. All current vaccines, however, are administered either orally, intramuscularly, or subcutaneously. We previously reported that epidermal powder immunization (EPI) with an extremely small dose of powdered influenza vaccine induces protective immunity in mice. In this study, we report that commonly used adjuvants can be used in EPI to further enhance the immune responses to an antigen. The IgG antibody response to diphtheria toxoid (DT) following EPI was augmented by 25- and 250-fold, when 1 mug DT was co-delivered with aluminum phosphate (alum) and a synthetic oligonucleotide containing **CpG** DNA motifs (**CpG** DNA), respectively. These antibodies had toxin-neutralization activity and were long lasting. Furthermore, EPI using an adjuvant selectively activated different subsets of T helper cells and gave either a **Th1** or a **Th2** type of immune response. Similar to needle injection into deeper tissues, EPI with alum adsorbed DT promoted a predominantly IgG1 subclass antibody response and elevated level of IL-4 secreting cells. These are indicative of Th2-type immunity. In contrast, co-delivery of **CpG** DNA adjuvant via EPI led to Th-1 type of response as characterized by the increased production of IgG2a antibodies and IFN-gamma secreting cells. This study indicated that EPI using appropriate adjuvants can produce an augmented antibody response and desirable cellular immune responses. EPI is a promising immunization method that may be used to administer a broad range of vaccines including vaccines with adjuvants.

L8 ANSWER 96 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 52
AN 2001:216325 BIOSIS

DN PREV200100216325
TI Mixed immune response induced in rodents by two naked DNA genes coding for mycobacterial glycosylated proteins.
AU Garapin, Axel-Claude; Ma, Laurence; Pescher, Pascale; Lagranderie, Micheline; Marchal, Gilles [Reprint author]
CS Unite de Physiopathologie de l'Infection, Institut Pasteur, 25 Rue du Dr Roux, 75724, Paris Cedex 15, France
gmarchal@pasteur.fr
SO Vaccine, (6 April, 2001) Vol. 19, No. 20-22, pp. 2830-2841. print.
CODEN: VACCDE. ISSN: 0264-410X.
DT Article
LA English
ED Entered STN: 2 May 2001
Last Updated on STN: 18 Feb 2002
AB Two genes of Mycobacterium tuberculosis, apa (Rv1860) and pro (Rv1796), coding for two glycosylated excreted proteins have been injected to mice and guinea pigs. They produce an extended immunological response of **Th1** and **Th2** types. Despite the fact that mycobacterial glycosylation is necessary for a high level of delayed-type hypersensitivity (DTH) reaction, plasmids bearing each of the two genes induced an elevated level of DTH sensitization. An inverse relation between the **CpG**-N hexamer cluster frequency and the protective effect of injected genes is described. A comparison of the strength of several eukaryotic promoters based on the diameter of the DTH reaction shows that CMVIE followed by the ubiquitin promoter are the most efficient among those tested. A significant protective effect (0.7 log unit CFU) in mice was found for the apa gene while the pro gene had no effect.

L8 ANSWER 97 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:258377 BIOSIS
DN PREV200100258377
TI Th1 cell regulation of mucosal IgA responses.
AU Boyaka, Prosper N. [Reprint author]; Lillard, James W., Jr.; Jackson, Raymond J. [Reprint author]; McGhee, Jerry R. [Reprint author]
CS UAB, 845, 19th Street South, Birmingham, AL, 34294-2170, USA
SO FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1043. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 30 May 2001
Last Updated on STN: 19 Feb 2002
AB Mucosal IgA Abs differ remarkably from all other isotypes and subclasses since no single **Th1** and **Th2** cytokine cells is strictly required for support of this response. Studies have shown a role for IL-4, IL-5, IL-6 and IL-10 in activation, division of committed IgA+ B cells and their terminal differentiation into IgA producing plasma cells. However, the exact Th1 cell cytokine and chemokine signals required for mucosal IgA responses are still unknown. We found that IL-12, which initiates Th1 cells, is an effective adjuvant when nasally co-administered with protein antigens and promotes mucosal IgA Ab responses. Two chemokines associated with Th1 cells, lymphotactin (lptn) and RANTES, also promote Th1-type and mucosal IgA responses to nasally co-administered protein antigens. However, lptn also induced some Th2-type cytokines. IL-12 deficient mice showed impaired Th1 cell and mucosal IgA Ab responses to an oral recombinant Salmonella vector expressing Tox C of tetanus toxin (rSalmonella Tox C). On the other hand, nasal immunization of these mice with **CpG** oligonucleotides (**CpG**) as adjuvant shifted the **CpG**-induced **Th1**-type responses toward **Th2** -type and preserved mucosal IgA Ab responses. These results show that

mucosal IgA responses can be induced by mucosal administration of IL-12 or the Th1 cell associated chemokines Ltn and RANTES. Further, together with the differential effect of IL-12 deficiency on the mucosal adjuvant activity of rSalmonella Tox C versus **CpG** they suggest that distinct Th1 cell programs support mucosal IgA responses. This issue is being addressed by analysis of chemokines produced by antigen-specific CD4+ Th1-type cells.

L8 ANSWER 98 OF 159 MEDLINE on STN DUPLICATE 53
AN 2002030416 MEDLINE
DN PubMed ID: 11757790
TI **CpG** oligodeoxynucleotides in asthma.
AU Hussain I; Kline J N
CS Department of Medicine, University of Iowa, Iowa City 52242. USA.. lftikhar-hussain@uiowa.edu
SO Current opinion in investigational drugs (London, England : 2000), (2001 Jul) 2 (7) 914-8. Ref: 39
Journal code: 100965718. ISSN: 1472-4472.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200206
ED Entered STN: 20020124
Last Updated on STN: 20020911
Entered Medline: 20020621
AB Asthma is a major health problem, of which the prevalence and severity are increasing, particularly in industrialized nations. One hypothesis for this is that diminished exposure to childhood infections in modern society has led to decreased Th1-type inflammation. Reduced **Th1** responses may lead to enhanced **Th2**-type inflammation, important in promoting asthma and allergic disease. The most common current treatment for asthma is corticosteroids; while these agents inhibit the function of inflammatory cells, they are ineffective in altering the initial Th2-type response to allergen in a sensitized individual. A novel therapeutic approach, recently reported in the preclinical setting, is the use of oligodeoxynucleotides (ODNs), which contain unmethylated motifs centered on CG dinucleotides. These **CpG** ODNs potently induce **Th1** cytokines and suppress **Th2** cytokines, and can prevent manifestations of asthma in animal models. These agents have the potential to reverse Th2-type responses to allergens and thus restore balance to the immune system. Clinical trials are ongoing.

L8 ANSWER 99 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:267700 BIOSIS
DN PREV200100267700
TI Parenteral and mucosal prime-boost immunization strategies in mice with hepatitis B surface antigen and **CpG** DNA.
AU McCluskie, Michael J. [Reprint author]; Weeratna, Risini D. [Reprint author]; Davis, Heather L. [Reprint author]
CS Coley Pharmaceutical Canada, 725 Parkdale Avenue, Ottawa, Ontario, K1Y 4E9, Canada
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A652. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 6 Jun 2001

Last Updated on STN: 19 Feb 2002

AB It has previously been demonstrated that synthetic oligodeoxynucleotides (ODN), containing immunostimulatory **CpG** motifs (**CpG** ODN), are a highly effective adjuvant when delivered by parenteral (intramuscular) or mucosal (oral, intranasal, intrarectal) routes. However, there have been no studies to date using combined parenteral/mucosal approaches with **CpG** DNA as adjuvant. In this study we evaluated different parenteral (IM) prime-mucosal (IN) boost and mucosal prime-parenteral boost strategies using hepatitis B surface antigen (HBsAg) alone or with different adjuvants: aluminum hydroxide (alum), cholera toxin (CT), **CpG** ODN. In addition, since **CpG** ODN has previously been shown to act synergistically with other adjuvants after parenteral or mucosal delivery, we also evaluated adjuvant combinations: alum + **CpG** ODN, and CT + **CpG** ODN. The effects of adjuvant and administration strategy on systemic and mucosal humoral responses were measured, as well as cell-mediated immune responses including T-cell proliferation and cytotoxic T lymphocyte (CTL) activity. These results were compared to parenteral only or mucosal only strategies. Our findings demonstrate that parenteral immunization can prime for mucosal responses even when different lymph nodes were being targeted. HBsAg-specific immune responses (IgG in plasma, CTL, T-cell proliferation) induced by parenteral prime could all be significantly enhanced by mucosal boosting and despite the fact that IM immunization alone could not induce mucosal IgA, it could prime for a subsequent mucosal boost. In addition, the presence of adjuvant at time of boosting could influence the nature of subsequent immune responses (**Th1** vs **Th2**). Mice primed IN could have their systemic immune responses boosted with a parenteral administration and surprisingly, it was also possible to enhance mucosal responses induced by IN prime with an IM boost. These results give an interesting insight into the understanding of immune activation by the different routes of vaccine delivery.

L8 ANSWER 100 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AN 2001:267699 BIOSIS

DN PREV200100267699

TI **CpG** containing DNA promotes Th1 responses, but fails to sustain long-lasting T cell memory.

AU Tian, Jide [Reprint author]; Olcott, Angelica [Reprint author]; Lu, Yuxin [Reprint author]; Hanssen, Lori [Reprint author]; Zekzer, Dan [Reprint author]; Ausubel, Lara [Reprint author]; Ornelas, Richard [Reprint author]; Melamed, Esther [Reprint author]; Quach, Phung [Reprint author]; Chaaban, Manar [Reprint author]; Kaufman, Daniel [Reprint author]

CS University of California Los Angeles, 10833 Le Conte Ave., Los Angeles, CA, 90095, USA

SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A652. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.

DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 6 Jun 2001
Last Updated on STN: 19 Feb 2002

AB Bacterial DNA containing **CpG** motifs has been shown to have strong adjuvanicity, and may help to provide a new generation of vaccines. However, little is known about the quality and quantity of long-term T cell memory responses, which are primed by antigen/DNA. Here, we examined the effects of antigen/DNA co-administration on T cell immunity in both **Th1**-biased and **Th2**-biased mice. Immunization of mice with antigen plus bacterial (plasmid pUC18), but not vertebrate DNA, primed a high frequency of Th1 cells and promoted the development of DTH

responses. Unexpectedly, the antigen/pUC18 primed Th1 responses declined rapidly after immunization and virtually disappeared after 8 weeks. In contrast, antigen/CFA primed T cells sustained a comparable level even at 12 weeks post immunization. Moreover, mice which had been presensitized with antigen/pUC18 failed to display a memory T cell response following rechallenge with antigen/CFA, and rather only displayed a primary T cell response. Together, these data suggest that **CpG** DNA can act as an adjuvant to prime Th1 responses, but fails to sustain long term T cell memory. Our findings provide new insights into **CpG**-DNA adjuvanicity and may aid in the design of future vaccination strategies for infectious diseases and cancer.

L8 ANSWER 101 OF 159 LIFESCI COPYRIGHT 2004 CSA on STN
AN 2001:75323 LIFESCI
TI Toll Meets Bacterial **CpG**-DNA
AU Wagner, H.
CS Institute of Medical Microbiology, Immunology and Hygiene, Technische Universitaet Muenchen, Trogerstrasse 9, 81675 Munich, Germany; E-mail: h.wagner@lrz.tu-muenchen.de
SO Immunity, (20010500) vol. 14, no. 5, pp. 499-502.
ISSN: 1074-7613.
DT Journal
TC General Review
FS F
LA English
SL English
AB Discovery of Drosophila Toll and its eight homologs coupled with identification of homologous mammalian Toll-like receptors (TLRs) that discriminate "self" from pathogen-derived ligands (also termed pathogen associated molecular patterns [PAMPs]) has rejuvenated research on "innate immunity." Today we have come to realize that, for the recognition of pathogens, plants and insects have relied for millions of years upon a system of receptors that share a characteristic cytoplasmatic domain now termed TIR (Toll/interleukin-1 receptor domain). Amazingly, the TIR domain has remained conserved, and it functions in antipathogen responses in plants, insects, and mammalians alike. In mammals, 10 Toll homologs (TLRs) have been identified so far, all of which appear to be type I integral membrane proteins with extracellular leucine-rich repeats (LRRs) and cytoplasmatic TIRs. It has also become clear that innate immune cells such as macrophages and dendritic cells (DCs) heavily impact on adaptive immune responses; innate immune cells control as antigen-presenting cells (APCs) whether T cells respond at all and whether emanating adaptive T cell responses become polarized toward **Th1** or **Th2**. Accordingly, we now argue that innate immunity was not only first but also effectively instructs subsequent adaptive responses to pathogens.

L8 ANSWER 102 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:278678 BIOSIS
DN PREV200100278678
TI In vivo induction of tolerance by an Ig-peptide is affected by **CpG** oligomers and Flt3 ligand treatments.
AU El-Amine, Moustapha [Reprint author]; Nguyen, Hao [Reprint author]; Scott, David W.
CS Holland Laboratory, American Red Cross, 15601 Crabbs Branch Way, Rockville, MD, 20855, USA
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A349. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English

ED Entered STN: 13 Jun 2001
Last Updated on STN: 19 Feb 2002

AB We have demonstrated that LPS lasts, transfected with a retrovirus encoding an Ig-peptide fusion protein, are tolerogenic in normal and even primed recipients. To study the influence of B-cell activators on Ig-peptide-induced tolerance induction, we stimulated murine (BALB/c) splenocytes with CD40L, **CpG** oligonucleotides or LPS. After 24hr, flow cytometry analysis using anti-MHCII and anti-B220 to monitor activation, showed a hierarchy with **CpG**>CD40L>LPS. These cells were then infected with IgG-peptide retrovirus, and injected into syngeneic recipients, which were challenged for tolerance. Our results showed that all APC, regardless of activation method, were tolerogenic at the humoral level. However, T-cell tolerance was not induced when **CpG** stimulated B cells were used as tolerogenic carriers, as measured by IL-2 and IL-4 cytokine responses. To further study the tolerogenic APC, we injected BM cells transduced with IgG-p12-26 peptide (or control IgG-OVA) into syngeneic recipients and then treated recipients with a 10-day course of Flt3L (10mug/animal). Flow cytometry, using anti-CD19 and anti-CD11c, established the efficacy of Flt3L to induce dendritic cells maturation in the spleen. Several weeks later, mice were challenged with p12-26 in CFA and T-cell tolerance was measured. Groups receiving IgG-12-26 and Flt3L were tolerant at a **Th1** level but surprisingly not at **Th2** T cell level, as measured by IL-4 secretion. These results show a possible immunogenicity of CD11c' APC in our system.

L8 ANSWER 103 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2002:201501 BIOSIS
DN PREV200200201501
TI Use of **CpG** as an adjuvant for a vaccine with the Chlamydia trachomatis mouse pneumonitis (MoPn) major outer membrane protein (MOMP).
AU Pal, S. [Reprint author]; Davis, H. L.; Peterson, E. M. [Reprint author]; De La Maza, L. M. [Reprint author]
CS University of California, Irvine, CA, USA
SO Abstracts of the General Meeting of the American Society for Microbiology, (2001) Vol. 101, pp. 311. print.
Meeting Info.: 101st General Meeting of the American Society for Microbiology. Orlando, FL, USA. May 20-24, 2001. American Society for Microbiology.
ISSN: 1060-2011.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 20 Mar 2002
Last Updated on STN: 20 Mar 2002

AB Oligonucleotides containing immunostimulatory **CpG** motifs have been shown to elicit systemic **Th1** and mucosal **Th2** immune responses. Recently, we have reported that a vaccine preparation of the C. trachomatis MOMP, using Freund's adjuvant, was able to protect mice against a genital challenge. The goal of this project was to determine if **CpG** could be used as an adjuvant for the MOMP to induce protection in mice against an intranasal (i.n.) challenge with C. trachomatis. One week-old BALB/c mice were immunized intramuscularly and subcutaneously with the MOMP and **CpG** suspended in aluminum hydroxide (Alhydrogel 85: Alum), and were subsequently boosted twice at 2 week intervals. Negative control mice were immunized with ovalbumin, **CpG** and Alum. Six weeks after the last immunization mice were challenged i.n. with 104 inclusion forming units (IFU) of C. trachomatis MoPn. Mice receiving MOMP/**CpG**/Alum had a strong immune response as shown by an ELISA serum antibody titer of 102,400. Following the i.n. challenge, mice immunized with the MOMP/**CpG**/Alum showed significantly less body weight loss when compared with control mice immunized with ovalbumin/**CpG**/Alum. By 10 days post-infection

the MOMP/**CpG**/Alum immunized mice had lost 5.2+-3.7% of their body weight while the controls had lost 26.3+-5.1% ($p<0.05$). Ten days after the challenge the mice were euthanized and the number of IFU in the lungs determined. The number of chlamydial IFU recovered from the mice inoculated with MOMP/**CpG**/Alum was significantly less (1.5+-0.5X106 per mouse) than the number of IFU detected in the mice inoculated with ovalbumin/**CpG**/Alum (47+-15X106 per mouse; $p<0.05$). This data suggests that **CpG** can be used as an effective adjuvant for the C. trachomatis MoPn MOMP to elicit a protective immune response against a chlamydial respiratory infection.

L8 ANSWER 104 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:463662 CAPLUS
DN 137:293467
TI Phosphorothioate oligonucleotides: looking for the motif(s) possessing immunostimulatory activities in humans
AU Brugnolo, Francesca; Annunziato, Francesco; Sampognaro, Salvatore; Manuelli, Cinzia; Cosmi, Lorenzo; Romagnani, Sergio; Maggi, Enrico; Parronchi, Paola
CS Department of Internal Medicine, University of Florence, Florence, Italy
SO Advances in Experimental Medicine and Biology (2001), 495(Progress in Basic and Clinical Immunology), 261-264
CODEN: AEMBAP; ISSN: 0065-2598
PB Kluwer Academic/Plenum Publishers
DT Journal
LA English
AB Phosphorothioate oligonucleotides (PS-ODNs) showed various effects on human cells, inducing B cell proliferation and production of cytokines from cells of innate immunity. PS-ODNs also shifted the functional profile of allergen-specific T cells from a prevalent **Th2** towards a prevalent **Th1**-like phenotype. These effects were independent of the absence or presence of classic **CpG** motifs, indicating that immunostimulatory sequences active in humans are different from those described in mice. PS-ODNs in which **CpG** dinucleotides were inverted into GpC still retained a significant effect on B and T cells.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 105 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 54
AN 2001:429147 BIOSIS
DN PREV200100429147
TI Immunostimulatory sequence DNA linked to the Amb a 1 allergen promotes **TH1** cytokine expression while downregulating **TH2** cytokine expression in PBMCs from human patients with ragweed allergy.
AU Marshall, Jason D.; Abtahi, Simin; Eiden, Joseph J.; Tuck, Stephen; Milley, Robert; Haycock, Fiona; Reid, Michael J.; Kagey-Sobotka, Anne; Creticos, Peter S.; Lichtenstein, Lawrence M.; Van Nest, Gary [Reprint author]
CS Dynavax Technologies Corp, 717 Potter St, Ste 100, Berkeley, CA, 94710, USA
SO Journal of Allergy and Clinical Immunology, (August, 2001) Vol. 108, No. 2, pp. 191-197. print.
CODEN: JACIBY. ISSN: 0091-6749.
DT Article
LA English
ED Entered STN: 12 Sep 2001
Last Updated on STN: 22 Feb 2002
AB Background: Recent studies have demonstrated that bacterially derived immunostimulatory sequences (ISSs) of DNA can activate the mammalian innate immune system and promote the development of TH1 cells. Promotion of TH1 immunity by means of immunotherapy in allergic patients has led to the alleviation of symptoms that result from allergen-specific TH2

responses. Objective: Our purpose was to investigate whether the TH1-enhancing properties of ISSs could be used to alter the TH2-dominated immune response of allergic PBMCs in vitro. Methods: Ragweed protein-linked **ISS** (PLI) was generated from a specific, highly active 22-base **ISS** and Amb a 1, the immunodominant allergen in ragweed pollen, to combine the TH1-enhancing properties of ISSs with allergen selectivity, and its activity was investigated in PBMC cultures from subjects with ragweed allergy. Results: PLI was markedly successful at reversing the dominant allergen-induced TH2 profile while greatly enhancing IFN-gamma production. Delivering ISSs in a linked form proved to be much more effective at modulating the resulting cytokine profile than delivering free ISSs in a mixture with unlinked Amb a 1. PLI also demonstrated cytokine-modulating properties, even when used to stimulate cells that had already been primed for 6 days with Amb a 1. The antigen specificity of the action of PLI was confirmed by the observations that PLI enhances Amb a 1-specific T-cell proliferation. Conclusion: These data indicate that delivery of ISSs within an antigen-specific context exhibits potent cytokine-modulating activity and, combined with its reduced allergenicity, makes this molecule a strong candidate for use in improved immunotherapy applications.

L8 ANSWER 106 OF 159 MEDLINE on STN DUPLICATE 55
AN 2001408845 MEDLINE
DN PubMed ID: 11292020
TI Eosinophil trafficking to sites of allergic inflammation.
AU Broide D; Sriramarao P
CS Department of Medicine, University of California San Diego, La Jolla 92093-0635, USA.. dbroide@ucsd.edu
NC AI 33977 (NIAID)
AI 35796 (NIAID)
AI 38425 (NIAID)
SO Immunological reviews, (2001 Feb) 179 163-72. Ref: 90
Journal code: 7702118. ISSN: 0105-2896.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200107
ED Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719
AB Eosinophils play a prominent pro-inflammatory role in allergic inflammation. Studies utilizing flow chambers, intravital video-microscopy, and cytokine and adhesion molecule-deficient mice have provided important insight into the mechanisms of eosinophil trafficking in inflamed blood vessels and into tissues in vivo. While the bone marrow generation of eosinophils is finely regulated by interleukin (IL)-5, the trafficking of eosinophils into tissues is regulated by several cytokines, chemokines, and adhesion molecules with overlapping functions. Prospects for therapeutically inhibiting eosinophilic inflammation by inhibiting eosinophil adhesion to endothelium are dependent on an improved understanding of the relative importance of individual cytokines and adhesion molecules in regulating eosinophil adhesion to endothelium. Alternative strategies to inhibit eosinophilic inflammation include the use of immunostimulatory DNA sequences containing a **CpG** motif to act as a **Th1** adjuvant to prevent **Th2** responses associated with IL-5 and eosinophilia. Immunostimulatory DNA sequences do not induce eosinophil apoptosis, but function at the level of the bone marrow to inhibit the IL-5-induced bone marrow generation and release of eosinophils.

L8 ANSWER 107 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 56
AN 2001:475424 BIOSIS
DN PREV200100475424
TI Modulation of gene-gun-mediated Th2 immunity to hepatitis B surface antigen by bacterial **CpG** motifs or IL-12.
AU Schirmbeck, Reinhold [Reprint author]; Reimann, Joerg
CS Institute for Medical Microbiology, University of Ulm, Albert Einstein Allee 11, D-89069, Ulm, Germany
reinhold.schirmbeck@medizin.uni-ulm.de
SO Intervirology, (March-June, 2001) Vol. 44, No. 2-3, pp. 115-123. print.
CODEN: IVRYAK. ISSN: 0300-5526.
DT Article
LA English
ED Entered STN: 10 Oct 2001
Last Updated on STN: 23 Feb 2002
AB Using different DNA vaccination techniques, we studied the IgG1/IgG2a antibody and MHC-I-restricted cytotoxic T lymphocyte (CTL) responses to the hepatitis B surface antigen (HBsAg) in mice. A single intramuscular injection of 100 mug HBs-Ag-encoding pCI/S plasmid DNA efficiently primed IgG2a antibody (IgG1/IgG2a ratio <0.3) and CTL responses to HBsAg (Th1 immunity). In contrast, a single intradermal injection of 1 mug of particle-coated pCI/S DNA with the gene-gun-primed IgG1 antibody responses to HBsAg (IgG1/IgG2a ratio >80) but there was no CTL response (Th2 immunity). Injection of immune-stimulating **CpG**-containing oligodeoxy-nucleotides (ODN) into the skin area used for gene-gun-mediated pCI/S DNA delivery shifted the polarization of the response towards Th1 immunity. A similar shift from **Th2** to **Th1** immunity was observed when the skin area used for gene-gun-mediated DNA transfer was conditioned by injection of recombinant IL-12. DNA vaccination can thus prime polarized immunity to HBsAg. The polarization of immunity is determined by the technique of plasmid DNA delivery as well as by conditions of the tissue into which DNA is inoculated. Th1 immunity to HBsAg (primed by injection of naked pCI/S DNA) dominated Th2 immunity (primed by gene-gun-mediated pCI/S DNA). In contrast, an established HBsAg-specific **Th2** immunity was readily shifted towards **Th1** immunity (including specific CTL priming) by an intramuscular boost injection of pCI/S DNA. These data contribute to the rational design of DNA vaccination strategies to efficiently prime anti-viral Th1 immune effector specificities using the gene gun.

L8 ANSWER 108 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:93809 CAPLUS
DN 135:194046
TI The immunostimulatory properties of bacterial DNA
AU Pisetsky, David S.
CS Durham VA Medical Center, Durham, NC, 27705, USA
SO Development of Novel Antimicrobial Agents: Emerging Strategies (2001), 71-80. Editor(s): Lohner, Karl. Publisher: Horizon Scientific Press, Wymondham, UK.
CODEN: 69AXXR
DT Conference; General Review
LA English
AB A review with 39 refs. Depending on base sequence, DNA can cause powerful immunostimulation and serve as a "danger signal" to activate host defense. In bacterial DNA, immunostimulation results from sequences of 6 bases that occur much more commonly in prokaryotic than eukaryotic DNA. These sequences, known as **CpG** motifs or immunostimulatory sequences (**ISS**), center on an unmethylated **CpG** dinucleotide and lead to the activation of B cells and macrophages as well as the production of cytokines such as IL-12, TNF-α and IFN-α/β. These cytokines can lead to Th1 cell predominance. In addition to **CpG** motifs, other DNA sequences such as runs of dG have immunostimulatory

activity. The properties of DNA as an immunomodulator are also influenced by backbone chemical since phosphorothioate oligonucleotides can cause potent immune stimulation. The immunostimulatory properties of DNA allow the design of novel therapeutic agents that can augment host defense during infection as well as influence the balance of **TH1/TH2** responses.

RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 109 OF 159 MEDLINE on STN DUPLICATE 57
AN 2001357881 MEDLINE
DN PubMed ID: 11418633
TI Novel roles of **CpG** oligodeoxynucleotides as a leader for the sampling and presentation of **CpG**-tagged antigen by dendritic cells.
AU Shirota H; Sano K; Hirasawa N; Terui T; Ohuchi K; Hattori T; Shirato K; Tamura G
CS First Department of Internal Medicine and Department of Dermatology, Tohoku University School of Medicine, Sendai, Japan.
SO Journal of immunology (Baltimore, Md. : 1950), (2001 Jul 1) 167 (1) 66-74. Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200109
ED Entered STN: 20010924
Last Updated on STN: 20010924
Entered Medline: 20010920
AB Oligodeoxynucleotides containing **CpG** motifs have been highlighted as potent Th1 activators. We previously reported that Ag and **CpG**, when conjugated together, synergistically promoted the Ag-specific **Th1** development and inhibited the **Th2** -mediated airway eosinophilia. In this study, we examined the mechanisms underlying the synergism of the covalent conjugation. The **CpG** -OVA conjugate enhanced the Th1 activation and development. These characteristic features of the conjugate could not be ascribed to the polymerization of OVA, but mirrored the augmented binding of the **CpG**-tagged Ag to dendritic cells (DCs) in a **CpG**-guided manner, because phycobiliprotein, R-PE, conjugated to **CpG** stained a higher proportion of DCs with higher intensity than the mixture. R-PE fluorescence was emitted from cytoplasmic portions of the DCs, which simultaneously expressed costimulatory molecules and IL-12. The **CpG**-conjugated R-PE trafficking described above actually served as a potent Ag. These results indicate that **CpG** conjugated to Ag exhibit novel joint properties as promoters of Ag uptake and DC activators, thereby potentiating the ability of DCs to generate Th1 cells. The DNA-mediated promotion of Ag uptake would be advantageous for evoking host immune responses against invading microorganisms.

L8 ANSWER 110 OF 159 MEDLINE on STN DUPLICATE 58
AN 2003062397 MEDLINE
DN PubMed ID: 12571984
TI Effect of immunostimulatory DNA sequence on the production of **Th1** and **Th2** cytokines induced by Dermatophagoides farinae allergen in vitro.
AU Zhou C; Yao H P; Wen T H; Sun C R
CS Institute of Infectious Diseases, First Affiliated Hospital of School of Medicine, Zhejiang University, Hangzhou 310003.
SO Zhongguo ji sheng chong xue yu ji sheng chong bing za zhi = Chinese journal of parasitology & parasitic diseases, (2001) 19 (2) 65-7. Journal code: 8709992. ISSN: 1000-7423.
CY China

DT Journal; Article; (JOURNAL ARTICLE)
LA Chinese
FS Priority Journals
EM 200310
ED Entered STN: 20030208
Last Updated on STN: 20031028
Entered Medline: 20031027
AB OBJECTIVE: To investigate the immunoregulatory effect of immunostimulatory DNA sequence (**ISS**) on the production of **Th1** and **Th2** cytokines induced by mite allergen in PBMC of the patients with mite allergic asthma in vitro. METHODS: PBMC from the patients with allergic asthma and normal controls were isolated and cultured in vitro stimulated by **ISS** and Dermatophagoides farinae allergen (Df). IL-12, IFN-gamma and IL-5 in the cell supernatants were detected by ELISA. Df specific IgE in sera of patients were assayed by fluorescent enzyme immunoassay. RESULTS: PBMC from both the patients and normal controls stimulated by **ISS** plus Df produced a significant increase in the level of both IFN-gamma and IL-12 compared with non-**ISS** and Df stimulations, whereas IL-5 was decreased. Moreover, the levels of IFN-gamma, IL-12 produced were significantly higher in normal controls than in the patients, on the contrary, IL-5 was down regulated. It was also shown that the level of IL-12 produced by PBMC of the patients with **ISS** plus Df stimulation correlated positively with that of IFN-gamma. CONCLUSION: **ISS** not only promotes the expressions of Th1 cytokines but also downregulates the production of Th2 cytokines induced by Df in both allergic and non-allergic individuals, indicating its potential application in the immunotherapy of mite allergy.

L8 ANSWER 111 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:922553 CAPLUS
DN 136:182149
TI **CpG** ODN can re-direct the Th bias of established Th2 immune responses in adult and young mice
AU Weeratna, Risini D.; Brazolot Millan, Cynthia L.; McCluskie, Michael J.; Davis, Heather L.
CS Coley Pharmaceutical Canada, Ottawa, ON, K1Y 4E9, Can.
SO FEMS Immunology and Medical Microbiology (2001), 32(1), 65-71
CODEN: FIMIEV; ISSN: 0928-8244
PB Elsevier Science B.V.
DT Journal
LA English
AB Induction of an appropriate immune response is essential for successful immunization. For example, Th1 type immune responses are necessary for the control of intracellular infections whereas Th2 type responses are more useful for the control of extracellular infections. Immunostimulatory **CpG** ODN (oligonucleotides containing unmethylated cytosine and guanine dinucleotides in specific base contexts) act as potent adjuvants and have been shown to induce Th1 type immune responses with a number of different antigens. This study investigates the effect of **CpG** ODN on the Th bias of immune responses generated against the hepatitis B major surface antigen (HBsAg) in adult (6-8 wk old) and young (<1 wk old) BALB/c mice. It also investigates the potential of **CpG** DNA to reverse a pre-established Th2 response generated as an adult or as a neonate, following re-exposure to HBsAg in adult life. Both adult and young mice immunized with HBsAg/**CpG** ODN had a Th1 biased immune response (strong cytotoxic T-lymphocyte (CTL) induction, IgG2a»IgG1). In contrast, mice immunized with HBsAg/alum had a Th2 type immune response (poor CTL, IgG1»IgG2a). More importantly, when animals were immunized with HBsAg/alum and boosted with HBsAg/**CpG** ODN, the **CpG** ODN were able to re-direct the Th2 response pre-established by alum, whereas the animals receiving the primary immunization with HBsAg/**CpG** ODN and later boosted with HBsAg/alum maintained their Th1 bias, even after the boost with alum.

These data suggest that **CpG** ODN have the ability to augment both humoral and cell mediated immune responses and override the Th2 bias created by alum, even in very young animals, which are known to have a Th2 biased immune system.

RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 112 OF 159 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2001294707 EMBASE
TI Manipulating the immune system: Humoral versus cell-mediated immunity.
AU McNeela E.A.; Mills K.H.G.
CS K.H.G. Mills, Infection and Immunity Group, Institute of Immunology, National University of Ireland, Kildare, Ireland. kingston.mills@may.ie
SO Advanced Drug Delivery Reviews, (23 Sep 2001) 51/1-3 (43-54).
Refs: 64
ISSN: 0169-409X CODEN: ADDREP
PUI S 0169-409X(01)00169-7
CY Netherlands
DT Journal; General Review
FS 026 Immunology, Serology and Transplantation
037 Drug Literature Index
039 Pharmacy
LA English
SL English
AB Many of the vaccines in use today were designed on an empirical basis with little understanding of the mechanism of protective immunity or knowledge of the protective antigens. Certain of these vaccines, based on killed or attenuated bacteria or viruses, are associated with unacceptable side-effects. New generation vaccines based on recombinant proteins or naked DNA have considerably improved safety profiles, but are often poorly immunogenic, especially when administered by mucosal routes. This is a particular problem with oral delivery; where high doses of antigen are required to generate even modest immune responses. In contrast, nasal delivery of antigens with a range of adjuvants or delivery systems has been shown to generate relatively potent immune responses and to protect against infection in animal models. Advances in immunology have demonstrated that a variety of cellular and humoral immune effector mechanisms, that are regulated by distinct **Th1** and **Th2** subtypes of T cells, mediate protection against different infectious diseases. The identification of adjuvants and immunomodulators, that can promote the selective induction of these distinct populations of T cells, has now made it possible to rationally design safe and effective mucosal vaccines against a range of infectious diseases of man. .COPYRGT. 2001 Elsevier Science B.V. All rights reserved.

L8 ANSWER 113 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 59
AN 2000-195254 [17] WPIDS
DNC C2000-060544
TI Immunostimulatory and immunoinhibitory stereoisomers of **CpG** oligonucleotides useful for immunotherapy of cancer.
DC B04 D16
IN KRIEG, A M
PA (CPGI-N) CPG IMMUNOPHARMACEUTICALS INC; (IOWA) UNIV IOWA RES FOUND
CYC 86
PI WO 2000006588 A1 20000210 (200017)* EN 88
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW

AU 9953238 A 20000221 (200029)
EP 1100807 A1 20010523 (200130) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2002521489 W 20020716 (200261) 104
AU 764532 B 20030821 (200359)

ADT WO 2000006588 A1 WO 1999-US17100 19990727; AU 9953238 A AU 1999-53238 19990727; EP 1100807 A1 EP 1999-938843 19990727, WO 1999-US17100 19990727; JP 2002521489 W WO 1999-US17100 19990727, JP 2000-562385 19990727; AU 764532 B AU 1999-53238 19990727

FDT AU 9953238 A Based on WO 2000006588; EP 1100807 A1 Based on WO 2000006588; JP 2002521489 W Based on WO 2000006588; AU 764532 B Previous Publ. AU 9953238, Based on WO 2000006588

PRAI US 1998-94370P 19980727

AB WO 200006588 A UPAB: 20000405

NOVELTY - Immunostimulatory and immunoinhibitory stereoisomers of **CpG** oligonucleotides are new.

DETAILED DESCRIPTION - New composition comprises an immunostimulatory or immunoinhibitory nucleic acid (NA) having a sequence including at least a sequence of formula (I):

5'-X1X2CGX3X4-3'

C and G = unmethylated;

X1-X4 = nucleotides, where at least two nucleotides have a phosphate backbone modification forming a chiral centre, and a number of the chiral centres have S chirality (immunostimulatory) or R chirality (immunoinhibitory).

An INDEPENDENT CLAIM is also included for a method for inducing antigen non-specific innate immune activation and broad-spectrum resistance to infectious challenge.

ACTIVITY - Cytostatic; Anti-asthmatic; Immunosuppressive; Anti-allergic; Immunostimulatory; Immunoinhibitory; Anti-inflammatory.

MECHANISM OF ACTION - Immunotherapy.

USE - The **immunostimulatory nucleic acid** can be co-administered with an antigen to a subject in a method for inducing an antigen-specific immune response in a subject. The **immunostimulatory nucleic acid** can also be used in methods for redirecting a subject's immune response from a **Th2** to a **Th1**, for treating asthma, for desensitizing a subject against the occurrence of an allergic reaction in response to contact with an allergen, for activating an immune cell, especially a lymphocyte or a dendritic cell expressing a cancer antigen or for treating cancer. The **immunostimulatory nucleic acid** is administered in conjunction with an anti-cancer therapy, especially an antibody, and is useful for increasing the responsiveness of a cancer cell to cancer therapy. The **immunostimulatory nucleic acid** can also be used in method to enhance recovery of bone marrow in a cancer therapy subject, to stimulate an immune response in a cancer subject, involving antigen dependent cellular cytotoxicity or for inducing cytokine production. It can also be used to stimulate natural killer cell lytic activity, to induce a Th1-type immune response or a mucosal immune response. The immunoinhibitory nucleic acid can be used to prevent an immune response, especially where the immune response in the subject is excessive due to having received an immune stimulating compound. The immunoinhibitory nucleic acid can be used to treat a subject having or at risk of an inflammatory disease, especially inflammatory bowel disease, autoimmune disease, gingivitis, psoriasis and sepsis (all claimed).

ADVANTAGE - None given.

Dwg.0/0

L8 ANSWER 114 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2000-524416 [47] WPIDS

CR 1997-145245 [13]; 1997-319766 [29]; 1998-101069 [09]; 1998-609243 [51]; 1999-095351 [08]; 1999-263358 [22]; 1999-313351 [26]; 2000-587434 [55];

2000-594650 [56]; 2001-050094 [06]; 2001-146289 [15]; 2001-367710 [38]; 2002-017124 [02]; 2002-017125 [02]; 2002-017215 [02]; 2002-083006 [11]; 2002-164363 [21]; 2002-194904 [25]; 2002-340184 [37]; 2002-393965 [42]; 2002-618960 [66]; 2003-066892 [06]; 2003-120675 [11]; 2003-182286 [18]; 2003-182497 [18]; 2003-416594 [39]; 2003-521577 [49]; 2003-556799 [52]; 2003-584406 [55]; 2003-669615 [63]; 2004-021946 [02]; 2004-088750 [09]; 2004-142653 [14]; 2004-168886 [16]; 2004-340011 [31]

DNC C2000-155775

TI Novel methods for obtaining polynucleotides with optimized immunomodulatory responses by directed evolution.

DC B04 C06 D16

IN SHORT, J M

PA (DIVE-N) DIVERSA CORP

CYC 90

PI WO 2000046344 A2 20000810 (200047)* EN 716
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000034839 A 20000825 (200059)
EP 1073710 A2 20010207 (200109) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2003524392 W 20030819 (200356) 627

ADT WO 2000046344 A2 WO 2000-US3086 20000204; AU 2000034839 A AU 2000-34839 20000204; EP 1073710 A2 EP 2000-913378 20000204, WO 2000-US3086 20000204; JP 2003524392 W JP 2000-597406 20000204, WO 2000-US3086 20000204

FDT AU 2000034839 A Based on WO 2000046344; EP 1073710 A2 Based on WO 2000046344; JP 2003524392 W Based on WO 2000046344

PRAI US 1999-246178 19990204

AB WO 200046344 A UPAB: 20040514

NOVELTY - Obtaining a polynucleotide (I) with an optimized immunomodulatory response, or that encodes a polypeptide with an optimized immunomodulatory response comprising creating a library of non-stochastically generated polynucleotides optimized by at least 1 directed evolution method, especially gene saturation mutagenesis and synthetic ligation polynucleotide reassembly, is new.

DETAILED DESCRIPTION - Novel method for obtaining an polynucleotide with an optimized immunomodulatory response, or that encodes a polypeptide with an optimized immunomodulatory response comprising creating a library of non-stochastically generated polynucleotides optimized by at least 1 directed evolution method including the introduction of mutations by non-stochastic methods (especially gene saturation mutagenesis) and by non-stochastic polynucleotide reassembly methods (especially synthetic ligation polynucleotide reassembly).

INDEPENDENT CLAIMS are also included for the following:

(1) obtaining a polynucleotide as in (I) comprising screening a library of non-stochastically generated polynucleotides and identifying a polynucleotide that has or encodes a polynucleotide with an optimized modulatory effect on an immune response;

(2) obtaining a polypeptide as in (I) comprising:

(a) creating a library of non-stochastically generated polynucleotides; and

(b) screening the library to identify a polynucleotide as in (I);

(3) obtaining an optimized polynucleotide that encodes an accessory molecule that improves the transport or presentation of antigens by a cell, comprising screening a library of non-stochastically generated polynucleotides optimized (for a human or animal) by directed evolution as in (I), for a polynucleotide that encodes a recombinant molecule that modulates antigen transport or presentation;

(4) obtaining an immunomodulatory polynucleotide with optimized

expression in a host comprising creating an optimized non-stochastically generated polynucleotide library as in (I);

(5) obtaining an immunomodulatory polynucleotide with optimized expression in a host comprising creating and optionally screening a library an optimized non-stochastically generated polynucleotide library;

(6) producing a progeny polynucleotide set comprising:

(a) annealing 2 primers to a circular parental polynucleotide, where the annealment regions of the polynucleotides are non-overlapping and 1 of the primers contains a non-stochastic mutagenic (optionally degenerate) cassette; and

(b) synthesizing a progeny polynucleotide for each primer by a polymerase-catalyzed amplification reaction, where the progeny polynucleotides may form a double-stranded mutagenized circular polynucleotide;

(7) producing progeny polypeptides containing a non-stochastic range of single amino acid substitutions from a template polypeptide, and optionally identifying desirable amino acid substitutions and combinations, comprising:

(a) amplifying a codon-containing template polynucleotide using a degenerate oligonucleotide for each codon to be mutated, where each oligonucleotide comprises a homologous sequence and (at least 1) degenerate trinucleotide cassette;

(b) subjecting the resultant progony polynucleotides to clonal amplification to express the encoded polypeptides; and optionally

(c) screening the progeny to identify those with a desirable change in at least 1 molecular property compared to the parent polynucleotide.

USE - The methods are useful for obtaining polynucleotide and polypeptides that can be used as genetic vaccines in the immunomodulation of humans and animals. The polynucleotides and peptides are preferably used as vaccines in the treatment, prevention or diagnosis of malaria. The methods are also useful for producing polynucleotides and/or polypeptides with enhanced (biological) properties, e.g. increased stability ex vivo (for increased shelf-life and ease of storage), stability in vivo (increased resistance to digestive acids and increased stability in circulation) (claimed), thermostable enzymes, improved vector transfer efficiency, improved immunogenicity, host (e.g. human) optimized vaccine (claimed) and targeted sequences.

Dwg.0/42

L8 ANSWER 115 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2000-514894 [46] WPIDS
DNC C2000-153644
TI Generating an anti-tumor cell immune response in a mammal through administration of a cationic molecule and immunologically active nucleic acid sequence without an expressible cDNA insert.
DC B01 B04 D16
IN KADHIM, S A; MIZZEN, L; SCHEULE, R K; YEW, N S
PA (GENZ) GENZYME CORP; (STRE-N) STRESSGEN BIOTECHNOLOGIES CORP
CYC 23
PI WO 2000045849 A2 20000810 (200046)* EN 40
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP US
AU 2000028703 A 20000825 (200059)
EP 1146907 A2 20011024 (200171) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2002536344 W 20021029 (200274) 49
ADT WO 2000045849 A2 WO 2000-US2943 20000204; AU 2000028703 A AU 2000-28703 20000204; EP 1146907 A2 EP 2000-907162 20000204, WO 2000-US2943 20000204; JP 2002536344 W JP 2000-596968 20000204, WO 2000-US2943 20000204
FDT AU 2000028703 A Based on WO 2000045849; EP 1146907 A2 Based on WO 2000045849; JP 2002536344 W Based on WO 2000045849
PRAI US 1999-118802P 19990205
AB WO 200045849 A UPAB: 20000921

NOVELTY - Generating an anti-tumor cell immune response in a mammal comprises administering to the mammal a composition comprising a complex of a cationic molecule and an immunologically active nucleic acid sequence without an expressible cDNA insert.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method of increasing the efficacy of a tumor antigen comprising administering an adjuvant comprising a cationic molecule:immunologically active nucleic acid sequence complex where the nucleic acid sequence is without an expressible cDNA insert; and

(2) a composition for generating a protective anti-tumor cell immune response in a mammal comprising a cationic molecule and an immunologically active nucleic acid sequence without an expressible cDNA insert.

ACTIVITY - Cytostatic; immunostimulant.

BALB/c mice were respectively inoculated intraperitoneally with AB12 mesothelioma cells on day 0. At three time points, days 6, 10 and 14, 5 groups of mice were dosed intraperitoneally with 50, 100 or 200 micro g genomic bacterial DNA cut into 4 kilobase (kb) fragments, with 100 micro l genomic bacterial DNA cut into 4 kb fragments complexed with cationic lipid GL 67 at a 1:4 molar ration (GL67:DNA) or with saline. There were no surviving mice from the control (saline) group 20 days after inoculation. A dose-dependent survival advantage of bacterial genomic DNA was seen with mice inoculated with 100 micro g bacterial DNA surviving until day 34 and mice inoculated with 200 micro g surviving until day 47. At day 60 post inoculation the group inoculated with GL67:DNA had a 100% survival rate.

MECHANISM OF ACTION - Gene therapy.

USE - The method is for generating a protective anti-tumor cell immune response in a mammal (claimed). The anti-tumor cell response generated may include an apoptotic response, anti-angiogenic response or inflammatory response, humoral response, a cellular response, a **Th1**-type response or a **Th2**-type response.

Dwg.0/7

L8 ANSWER 116 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:741936 CAPLUS
DN 133:308997
TI Methods for skewing the balance between **Th1** and **Th2** immune responses
IN Bottomly, H. Kim; Caplan, Michael J.; Sosin, Howard B.
PA Panacea Pharmaceuticals, LLC, USA
SO PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000061157	A1	20001019	WO 2000-US9270	20000407
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2002090381	A1	20020711	US 1999-290029	19990409
PRAI	US 1999-290029	A	19990409		

AB The present invention provides compns. and methods for regulating immune system reactions by biasing T cell responses away from **Th1** or **Th2** responses in a pre-determined manner. Control is effected at the stage of antigen/APC encounter and/or at the stage of APC/T cell

encounter. In preferred embodiments, a **Th1** or **Th2** response is inhibited through induction of the alternative response. The inventive methods and reagents are particularly useful for the management of autoimmune disorders, allergy, and asthma.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 117 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:376624 BIOSIS
DN PREV200000376624
TI Effects of **CpG** DNA on **Th1/Th2** balance in asthma.
AU Kline, J. N. [Reprint author]
CS Division of Pulmonary Medicine, Univesity of Iowa College of Medicine, 200 Newton Drive, C33GH UIHC, Iowa City, IA, 52242, USA
SO Wagner, H. Curr. Top. Microbiol. Immunol., (2000) pp. 211-225. Current Topics in Microbiology and Immunology; Immunobiology of bacterial CpG-DNA. print.
Publisher: Springer-Verlag, Heidelberger Platz 3, D-1000, Berlin, 33, Germany. Series: Current Topics in Microbiology and Immunology.
CODEN: CTMIA3. ISSN: 0070-217X.
DT Book
Book; (Book Chapter)
LA English
ED Entered STN: 6 Sep 2000
Last Updated on STN: 8 Jan 2002

L8 ANSWER 118 OF 159 AGRICOLA Compiled and distributed by the National Agricultural Library of the Department of Agriculture of the United States of America. It contains copyrighted materials. All rights reserved. (2004) on STN
AN 2000:38243 AGRICOLA
DN CAT11067519
TI Immunobiology of bacterial **CpG**-DNA.
AU Wagner, H.
AV DNAL (QR1.C8 no. 247)
SO 2000 viii, 260 p. : ill. ; 24 cm
Publisher: Berlin ; New York : Springer, 2000.
Series: Current topics in microbiology and immunology, 247
ISBN: 3540664009.
NTE Includes bibliographical references and index.
Mechanism of action of **CpG** DNA / A.M. Krieg, G. Hartmann, and A.-K. Yi -- Oligodeoxyribonucleotides with 5'-ACGT-3' or 5'-TCGA-3' sequence induce production of interferons / S. Yamamoto, T. Yamamoto, and T. Tokunaga -- Macrophage activiation by immunostimulatory DNA / K.J. Stacey ... [et al.] -- Consequences of bacterial **CpG** DNA-driven activation of antigen-presenting cells / T. Sparwasser and G.B. Lipford -- Signal transduction pathways activated by **CpG**-DNA / H. Hacker -- **CpG** DNA co-stimulates antigen-reactive T cells / K. Heeg -- Role of type I interferons in T cell activation induced by **CpG** DNA / S. Sun and J. Sprent -- Hematopoietic remodeling triggered by **CpG** DNA / G.B. Lipford and T. Sparwasser -- **CpG** DNA augments the immunogenicity of plasmid DNA vaccines / D.M. Klinman, K.J. Ishii, and D. Verthelyi -- The role of bacterial DNA in autoantibody induction / D.S. Pisetsky -- **CpG** DNA in cancer immunotherapy / G.J. Weiner -- Use of **CpG** DNA for enhancing specific immune responses / H.L. Davis -- Immunostimulatory-sequence DNA is an effective mucosal adjuvant / A.A. Horner and E. Raz -- **CpG** DNA switches on Th1 immunity and modulates antigen-presenting cell function / R.S. Chu, D. Askew, and C.V. Harding -- Effects of **CpG** DNA on **Th1/Th2** balance in asthma / J.N. Kline -- Responses of human B cells to DNA and phosphorothioate oligodeoxyribonucleotides / H. Liang and P.E. Lipsky.
CY Germany

DT Bibliography; (MONOGRAPH)
FS Non-U.S. Imprint other than FAO
LA English

L8 ANSWER 119 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 60
AN 2000:174347 BIOSIS
DN PREV200000174347
TI **CpG** DNA induces stronger immune responses with less toxicity than other adjuvants.
AU Weeratna, Risini D.; McCluskie, Michael J.; Xu, Yu; Davis, Heather L. [Reprint author]
CS Loeb Health Research Institute at the Ottawa Hospital, 725 Parkdale Avenue, Ottawa, ON, K1Y 4E9, Canada
SO Vaccine, (March 6, 2000) Vol. 18, No. 17, pp. 1755-1762. print.
CODEN: VACCDE. ISSN: 0264-410X.
DT Article
LA English
ED Entered STN: 3 May 2000
Last Updated on STN: 4 Jan 2002
AB The ability to augment protective immune responses with minimal side effects is quintessential for a good adjuvant. This study has compared various adjuvants that are used in animal research (Freund's complete and incomplete adjuvants, Titermax Gold), are licensed for human use (alum), or are in clinical testing for humans (monophosphoryl lipid, **CpG** DNA), for their ability to augment humoral responses to a model antigen (hepatitis B surface antigen) and for the degree of damage they caused in the injected muscle. According to the data, the adjuvant combination **CpG** DNA+alum had the greatest potential to augment immune responses with minimal side effects at the injection site. Evaluation of antibody isotypes indicated Th2 responses (no IgG2a) with all adjuvants except monophosphoryl lipid and **CpG** DNA, which gave mixed **Th1/Th2** responses (IgG1 and IgG2a). Strong Th1 responses (predominantly IgG2a) were obtained with combinations of **CpG** DNA with other adjuvants.

L8 ANSWER 120 OF 159 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2000315907 EMBASE
TI Genetic immunisation and treatment of disease.
AU Kang C.U.; Weiner D.B.; Boyer J.D.
CS J.D. Boyer, Dept. of Pathology/Laboratory Med., Univ. of Pennsylvania Sch. of Med., Philadelphia, PA 19104, United States
SO Expert Opinion on Therapeutic Patents, (2000) 10/9 (1345-1355).
Refs: 17
ISSN: 1354-3776 CODEN: EOTPEG
CY United Kingdom
DT Journal; General Review
FS 022 Human Genetics
026 Immunology, Serology and Transplantation
037 Drug Literature Index
039 Pharmacy
LA English
SL English
AB Alternative approaches to the more traditional treatments of cancer, allergies and autoimmune diseases are being pursued. In addition, new modes of vaccination are under development. DNA delivery (genetic immunisation) is among the new technologies being investigated. This technique of injecting DNA induces both cellular and humoral responses, can lead to active protein production in vivo and is highly adaptable to the requirements of the condition being targeted. The genes can be delivered such that the immune responses can be polarised to either a **Th1** or **Th2** phenotype. The manipulation of the immune

response can be accomplished by a variety of methods including mode of delivery and use of cytokine genes. Delivery of DNA directly to a host has a great deal of potential with regard to therapy and vaccine development. This potential is apparent based on the extensive number of patents which have been awarded over the past three years.

L8 ANSWER 121 OF 159 MEDLINE on STN DUPLICATE 61
AN 2000405290 MEDLINE
DN PubMed ID: 10903720
TI **CpG**-DNA-mediated transient lymphadenopathy is associated with a state of Th1 predisposition to antigen-driven responses.
AU Lipford G B; Sparwasser T; Zimmermann S; Heeg K; Wagner H
CS Institute for Medical Microbiology, Immunology and Hygiene, Klinikum Rechts der Isar, Technical University of Munich, Munich, Germany.. G.B.Lipford@lrz.tum.de
SO Journal of immunology (Baltimore, Md. : 1950), (2000 Aug 1) 165 (3) 1228-35.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; AIDS
EM 200008
ED Entered STN: 20000901
Last Updated on STN: 20000901
Entered Medline: 20000822
AB Infections can influence concurrent and subsequent **Th1** vs **Th2** immune responses to Ags. Through pattern recognition of foreign unmethylated **CpG** dinucleotides, the vertebrate innate immune system can sense infectious danger and typically replies with a Th1-polarized adaptive immune response. We examined whether **CpG** -DNA exposure would influence subsequent responses to infection and soluble Ags. **CpG**-DNA injection led to local lymphadenopathy characterized by maintenance of cellular composition with some biasing toward elevated dendritic cell composition. Sustained local production of IL-12 and IFN-gamma from dendritic cells and T cells was shown. Prior injection by up to 2 wk with **CpG**-DNA protected BALB/c mice from Th2 driven lethal leishmaniasis. **CpG**-DNA injection by up to 5 wk before soluble Ag challenge resulted in the generation of Ag-specific CTL, Th1 recall responses to Ag, and Th1-polarized Ag-specific Absolute Thus, **CpG**-DNA instigated a local predisposition for intense CTL responses and Th1-polarized immune responses to subsequent infections or Ag challenge. The induction by the innate immune system of a locally contained hypersensitivity could represent a capacitating immune reaction yielding rapid conditioned responses to secondary infections.

L8 ANSWER 122 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 62
AN 2001:56772 BIOSIS
DN PREV200100056772
TI **CpG** DNA is an effective oral adjuvant to protein antigens in mice.
AU McCluskie, Michael J.; Weeratna, Risini D.; Krieg, Arthur M.; Davis, Heather L. [Reprint author]
CS Loeb Health Research Institute, Ottawa Hospital, 725 Parkdale Avenue, Ottawa, Ont, K1Y 4E9, Canada
hdavis@lri.ca
SO Vaccine, (22 November, 2000) Vol. 19, No. 7-8, pp. 950-957. print.
CODEN: VACCDE. ISSN: 0264-410X.
DT Article
LA English
ED Entered STN: 24 Jan 2001
Last Updated on STN: 12 Feb 2002

AB We have previously reported that synthetic oligodeoxynucleotides containing immunostimulatory **CpG** motifs (**CpG** ODN) are potent adjuvants to protein administered by intramuscular (IM) injection or intranasal (IN) inhalation to BALB/c mice. Herein, we have evaluated oral delivery of **CpG** ODN with purified hepatitis B surface antigen (HBsAg) or tetanus toxoid (TT) to determine its potential as an adjuvant to oral vaccines. **CpG** ODN augmented systemic (IgG in plasma, CTL, T-cell proliferation) and mucosal (IgA in lung, vaginal or gut washes, feces and saliva) immune responses against both antigens. **CpG** stimulated both T-helper type 1 (**Th1**) (CTL, IgG2a) and **Th2** (IgG1, IgA) responses when delivered orally. Results from this study indicate that stimulatory **CpG** ODN may be effective as an adjuvant with oral vaccines.

L8 ANSWER 123 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 63
AN 2000:494966 BIOSIS
DN PREV200000495087
TI The immunobiology and clinical potential of immunostimulatory **CpG** oligodeoxynucleotides.
AU Weiner, George J. [Reprint author]
CS C.E. Block Professor of Cancer Research and Internal Medicine, 5970Z JPP, University of Iowa Cancer Center, University of Iowa, 200 Hawkins Drive, Iowa City, IA, 52242, USA
SO Journal of Leukocyte Biology, (October, 2000) Vol. 68, No. 4, pp. 455-463. print.
CODEN: JLBIE7. ISSN: 0741-5400.
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 15 Nov 2000
Last Updated on STN: 10 Jan 2002
AB Over 100 years ago, Coley first explored the use of bacterial products as immunostimulatory therapy for nonbacterial disease. It is now clear that bacterial DNA, and synthetic oligodeoxynucleotides containing specific motifs centered on a **CpG** dinucleotide (**CpG** ODN), are potent immunostimulatory agents. The molecular mechanisms responsible for the immunostimulatory effects of **CpG** ODN have yet to be elucidated fully, although it is clear that **CpG** ODN act rapidly on a variety of cell types. This includes activation of B cells, natural killer cells, and antigen-presenting cells including monocytes, macrophages, and dendritic cells. These effects have led to evaluation of **CpG** ODN as immune adjuvants in immunization where they have been shown in animal models to enhance the development of a TH1-type immune response. Preliminary results from clinical trials using **CpG** ODN as an immune adjuvant are promising. Preclinical studies suggest **CpG** ODN can also enhance innate immunity against a variety of infections, synergize with monoclonal antibody to enhance antibody-dependent cellular cytotoxicity, and alter the **Th1**/**Th2** balance as a possible treatment for allergic diseases and asthma. Clinical evaluation has recently begun to determine whether promising preclinical results with **CpG** ODN can be translated into effective and tolerable clinical treatment approaches.

L8 ANSWER 124 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:444425 CAPLUS
DN 134:99149
TI Stimulation of the innate immune system: a paradigm for the future identification of disease modifying agents to treat asthma and allergic diseases
AU Williams, Robert J.
CS Aventis Pharmaceuticals, Essex, RM10 7XS, UK
SO Emerging Therapeutic Targets (2000), 4(3), 313-321

CODEN: ETTAF7; ISSN: 1460-0412
PB Ashley Publications Ltd.
DT Journal; General Review
LA English
AB A review and discussion with 65 refs. Asthma and allergic diseases in general have reached epidemic proportions in the developed world. Current asthma therapy relies heavily on the prophylactic use of anti-inflammatory corticosteroids administered by inhalation. However, concerns remain regarding the side effect profile of these agents and also their efficacy in controlling disease in many patients. Epidemiol. studies have suggested a link between lack of exposure to bacteria and the rising incidence of allergic diseases. Furthermore, recent animal studies have clearly shown that administration of bacteria or bacterial components, notably DNA, can suppress allergen-induced lung inflammation. Most noteworthy is the observation that the anti-inflammatory effects of bacterial DNA sequences containing unmethylated CG dinucleotides (**CpG** motifs) can be long lasting. This observation has led to the suggestion that therapies based on these or related mols. may potentially be disease modifying. The mechanisms invoked to explain this phenomenon relate to stimulation of cytokine production, notably IL-12, by cells of the innate immune system. This appears to lead to generation of **Th1**- rather than **Th2**-type immunol. memory to potential allergens and also the generation of suppresser T-lymphocyte subsets. Data reported for compds. of the imidazoquinoline class has demonstrated that it is possible to identify low mol. weight compds. with similar anti-allergic properties. Development of our understanding of the cellular and mol. basis for the anti-allergic properties of bacterially-derived immunostimulants and related mols. is likely to lead to the identification of new, potentially disease modifying therapies for the treatment of asthma and allergic diseases.
RE.CNT 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 125 OF 159 MEDLINE on STN DUPLICATE 64
AN 2000154380 MEDLINE
DN PubMed ID: 10689790
TI Effects of **CpG** DNA on **Th1/Th2** balance in asthma.
AU Kline J N
CS Division of Pulmonary Medicine, University of Iowa College of Medicine, Iowa City 52242, USA.. joel-kline@uiowa.edu
SO Current topics in microbiology and immunology, (2000) 247 211-25. Ref: 52
Journal code: 0110513. ISSN: 0070-217X.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; AIDS
EM 200004
ED Entered STN: 20000427
Last Updated on STN: 20000427
Entered Medline: 20000414
AB Thus, in our studies, we demonstrated that **CpG** ODN are effective in preventing the development of eosinophilic airway inflammation and bronchial hyper-reactivity in a murine model of asthma. Antigen-associated elevation of serum IgE levels is also suppressed. **CpG** ODN, administered in conjunction with antigen, is also effective in down-regulation of established Th2 responses. This protection is neither murine strain-dependent nor model-dependent. Although these effects of **CpG** ODN are associated with the induction of the Th1 cytokines IFN-gamma and IL-12, neither cytokine is absolutely required for the protection. These results suggest that

CpG ODN may be an effective immunomodulatory agent in the treatment, and possibly prevention, of asthma.

L8 ANSWER 126 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 65
AN 2000:166468 BIOSIS
DN PREV200000166468
TI Correlation between DNA methylation and murine IFN-gamma and IL-4 expression.
AU Falek, Paula R.; Ben-Sasson, Shlomo Z. [Reprint author]; Ariel, Mira
CS Lautenberg Center for General and Tumor Immunology, Hebrew University-Hadassah Medical Center, Jerusalem, 91120, Israel
SO Cytokine, (March, 2000) Vol. 12, No. 3, pp. 198-206. print.
CODEN: CYTIE9. ISSN: 1043-4666.
DT Article
LA English
ED Entered STN: 3 May 2000
Last Updated on STN: 4 Jan 2002
AB In order to determine the possible role of DNA methylation as a regulatory mechanism for the restricted pattern of lymphokine production among differentiated **Th1** and **Th2** cells, we examined the extent of methylation of the interferon gamma (IFN-gamma) and the interleukin 4 (IL-4) genes in fresh activated murine Th0, **Th1** and **Th2** cells, unstimulated naive T cells, B cells, bone marrow derived non-B non-T cells, thymocytes and liver. All of the **CpG** dinucleotides examined in the IL-4 and the IFN-gamma genes, were fully methylated over the body of the gene in all of the examined cells. However, analysis of the promoter regions of these genes revealed a different pattern. While the IL-4 promoter is fully methylated in all of the examined cells, two adjacent **CpG** dinucleotides near the initiation point of the IFN-gamma gene were unmethylated in all T cells, including 17-day-old fetal thymocytes. In contrast, B cells, bone marrow non-B non-T cells and liver cells displayed a full methylated profile of the IFNgamma promoter. These results suggest that the mutually exclusive pattern of IFNgamma and IL-4 production in **Th1** and **Th2** cells is not regulated by differential demethylation of these two genes.

L8 ANSWER 127 OF 159 MEDLINE on STN DUPLICATE 66
AN 2001193548 MEDLINE
DN PubMed ID: 11217440
TI [New immunotherapeutic approaches for the treatment of anaplastic large cell lymphoma in a mouse model].
Neue immuntherapeutische Ansatze des grosszelligen anaplastischen Lymphoms in einem Maus-Modell.
AU Bittner C; Merz H; Krokowski M; Briese J; Wiedemann G J; Feller A C
CS Institut fur Pathologie, Universitatsklinikum Lubeck.
SO Verhandlungen der Deutschen Gesellschaft fur Pathologie, (2000) 84 187-98.
Journal code: 7503704. ISSN: 0070-4113.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA German
FS Priority Journals
EM 200104
ED Entered STN: 20010410
Last Updated on STN: 20010410
Entered Medline: 20010405
AB As there is still a high mortality of the large cell anaplastic non Hodgkin lymphoma (ALCL) (between 40-70%, depending on prognostic factors) there is a need for new therapeutic approaches. Therefore, we studied different strategies for cancer immunotherapy in an immunogenic ALCL tumor model system: A murine IL-9 dependent T cell line was transfected with IL-9 cDNA, resulting in an autonomous growing T cell line designated G6BB, which had a high tumor incidence after injecting of as few as 10(4) cells

subcutaneously into syngeneic C57Bl/6 mice. Tumor growth, dissemination, histology, and immunohistochemistry were similar to human ALCL. This mouse model provides an immunogenic in vivo system to investigate antitumor immunotherapies. In order to increase antigen recognition by T cells and T cell activation, we administered tumor bearing mice cell-based cancer vaccines with irradiated tumor cells alone or in combination with immunostimulating **CpG**-Oligonucleotides, a combination of **Th1** cytokines and **Th2** cytokine antibodies (IL-12, IFN-gamma, GM-CSF, Anti-IL-10) (after detecting a Th2 cytokine profile in G6BB), or the recall antigens diphtheria, pertussis, and tetanus.

L8 ANSWER 128 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:138250 CAPLUS
DN 132:264014
TI Regulation of T-helper type 2 cell and airway eosinophilia by transmucosal coadministration of antigen and oligodeoxynucleotides containing **CpG** motifs
AU Shirota, Hidekazu; Sano, Kunio; Kikuchi, Tadashi; Tamura, Gen; Shirato, Kunio
CS First Department of Internal Medicine, Tohoku University School of Medicine, Sendai, 980-8574, Japan
SO American Journal of Respiratory Cell and Molecular Biology (2000), 22(2), 176-182
CODEN: AJRBEL; ISSN: 1044-1549
PB American Thoracic Society
DT Journal
LA English
AB The characteristic features of bronchial asthma, including airway eosinophilia and elevated IgE levels, are known to be orchestrated by T-helper (Th) 2 cells. Oligodeoxynucleotides containing **CpG** motifs (**CpG**) have recently been highlighted as an immunomodulator that biases toward a Th1-dominant phenotype. However, **CpG** may incur nonspecific Th1 activation and toxic effects. In this study we report a novel inhibition of Th2 cells by transmucosal inoculation of antigen and **CpG**. Intratracheal instillation of **CpG** inhibited airway eosinophilia and Th2 cytokine production in antigen-sensitized mice. The inhibition was observed when **CpG** was given at the same time or in advance of antigen challenge. Notably, concomitant administration of **CpG** and antigen (as opposed to either one alone) was essential for the inhibitory effects. The antigen dose could be minimized to avoid a harmful boost of eosinophilia. **CpG** had few effects on systemic anti-ovalbumin IgE responses. These results demonstrate that a synergism between transmucosally administered allergen and **CpG** inhibits Th2 cells in parallel with an improvement in airway eosinophilia and hyperresponsiveness without impeding systemic immune responses. Our data imply that inhalation of a minimal amount of allergen plus **CpG** could be a novel desensitization therapy for patients with bronchial asthma.
RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 129 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:268089 CAPLUS
DN 133:265321
TI **CpG** DNA as a Th1 trigger
AU Heeg, Klaus; Zimmermann, Stefan
CS Institute of Medical Microbiology and Hygiene, Philipps University of Marburg, Marburg, D-35037, Germany
SO International Archives of Allergy and Immunology (2000), 121(2), 87-97
CODEN: IAAIEG; ISSN: 1018-2438
PB S. Karger AG
DT Journal; General Review
LA English

AB A review with 128 refs. Over the last few years, it has been recognized that along with structural components and products of bacteria, bacterial DNA is also capable of signaling infectious danger to cells of the innate immune system. Particular DNA sequences (**CpG** motifs), which are abundant in prokaryotic (bacterial) but not in mammalian DNA, cause the activation and stimulation of immune cells. Research has been catalyzed by the finding that certain synthetic oligodeoxynucleotides mimic the action of bacterial DNA. Immunostimulation induced by bacterial DNA or synthetic oligonucleotides not only contributes to the knowledge of the pathogen-host interrelationship during infection, but can also be used therapeutically to condition or modify ongoing immune responses of the adaptive immune system. Accordingly, **CpG** motifs have been used as vaccine adjuvants as well as instructing agents to selectively induce Th1-dominated immune responses. Hence, **CpG** motifs might be used in the future as adjuvants and/or immunomodulatory agents to treat or prevent undesired Th2-dominated immune responses, such as allergy.
RE.CNT 126 THERE ARE 126 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 130 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:140213 BIOSIS
DN PREV200000140213
TI **ISS** conjugated to Amb a 1 allergen promotes a **Th2** to **Th1** switch in PBMC from ragweed-allergic humans.
AU Marshall, J. D. [Reprint author]; Eiden, J. J. [Reprint author]; Kagey-Sobotka, A.; Creticos, P. S.; Lichtenstein, L. M.; Van Nest, G. [Reprint author]
CS Dynavax Technologies Corporation, Berkeley, CA, USA
SO Journal of Allergy and Clinical Immunology, (Jan., 2000) Vol. 105, No. 1 part 2, pp. S76-S77. print.
Meeting Info.: 56th Annual Meeting of the American Academy of Allergy, Asthma and Immunology. San Diego, California, USA. March 03-08, 2000. American Academy of Allergy, Asthma and Immunology.
CODEN: JACIBY. ISSN: 0091-6749.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 19 Apr 2000
Last Updated on STN: 4 Jan 2002

L8 ANSWER 131 OF 159 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 67
AN 2000054147 EMBASE
TI Genetic and environmental factors contributing to the onset of allergic disorders.
AU Parronchi P.; Brugnolo F.; Sampognaro S.; Maggi E.
CS Dr. E. Maggi, Dipartimento di Medicina Interna, Sez. Immunoallergol. Malatt. Respir., Policlinico di Careggi, I-50134 Firenze, Italy. e.maggi@mednuc2.dfc.unifi.it
SO International Archives of Allergy and Immunology, (2000) 121/1 (2-9). Refs: 88
ISSN: 1018-2438 CODEN: IAAIEG
CY Switzerland
DT Journal; General Review
FS 005 General Pathology and Pathological Anatomy
017 Public Health, Social Medicine and Epidemiology
022 Human Genetics
026 Immunology, Serology and Transplantation
LA English
SL English
AB Evidence has been accumulated to suggest that allergen-reactive Th2 cells play a triggering role in the activation and/or recruitment of IgE antibody-producing B cells, mast cells and eosinophils, the cellular triad

involved in allergic inflammation. Recently, chemokines and chemokine receptors involved in such Th2-type response have been also defined. Th2 cells represent the polarized arm of the effector-specific responses that contribute to the protection against gastrointestinal nematodes and act as regulatory cells for chronic and/or excessive **Th1**-mediated responses. **Th2** cells are generated from precursor naive Th cells when they encounter the specific antigen in an IL-4-containing microenvironment. The question of how these Th2 cells are selected in atopic patients is also unclear. Both the nature of the T cell receptor signalling provided by the allergen peptide ligand and a disregulation of IL-4 production likely concur to determine the Th2 profile of allergen-specific Th cells, but the genetic unbalanced IL-4 production is certainly overwhelming. Some gene products selectively expressed in Th2 cells or selectively controlling the expression of IL-4 have recently been described. These findings allow to suggest that the upregulation of genes controlling IL-4 expression and/or abnormalities of regulatory mechanisms of Th2 development and/or function may be responsible for Th2 responses against allergens in atopic people. The increasing prevalence of allergy in developed countries suggests that environmental factors acting either before or after birth also contribute to regulate the development of Th2 cells and/or their function. The reduction of infectious diseases in early life due to increasing vaccinations, antimicrobial treatments as well as changed lifestyle are certainly important in influencing the individual outcome in the Th response to ubiquitous allergens. Moreover, the recent evidence that bacterial DNA or oligodeoxynucleotides containing unmethylated '**CpG** motifs' promote the development of Th1 cells via the production of immunomodulatory cytokines (namely IL-12, IL-18 and IFNs) by professional antigen-presenting cells confirms previous epidemiological data. The new insight into the pathophysiology of T cell responses in atopic diseases provides exciting opportunities for the development of novel immunotherapeutic strategies. Copyright (C) 2000 S. Karger AG, Basel.

L8 ANSWER 132 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1999-508645 [42] WPIDS
CR 1999-508653 [42]; 1999-518452 [43]; 1999-527366 [44]
DNN N1999-379024 DNC C1999-148625
TI Identifying nucleic acid that directly or indirectly modulates the immune response to a genetic vaccine vector, e.g. for prevention of infection or cancer.
DC B04 D16 S03
IN HOWARD, R; PUNNONEN, J; STEMMER, W P C; WHALEN, R G; PATTEN, P A; BASS, S H
PA (MAXY-N) MAXYGEN INC; (HOWA-I) HOWARD R; (PUNN-I) PUNNONEN J; (STEM-I) STEMMER W P C; (WHAL-I) WHALEN R G
CYC 85
PI WO 9941368 A2 19990819 (199942)* EN 104
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
AU 9926741 A 19990830 (200003)
EP 1053312 A2 20001122 (200061) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 2001006950 A1 20010705 (200139)
JP 2002507392 W 20020312 (200220) 132
JP 2002507393 W 20020312 (200220) 188
AU 2002027579 A 20020516 (200244)#
AU 2002027613 A 20020516 (200244)#
AU 2002027677 A 20020516 (200244)#
MX 2000007892 A1 20011101 (200279)

MX 2000007889 A1 20020901 (200370)

ADT WO 9941368 A2 WO 1999-US3020 19990210; AU 9926741 A AU 1999-26741 19990210; EP 1053312 A2 EP 1999-906948 19990210, WO 1999-US3020 19990210; US 2001006950 A1 Provisional US 1998-74294P 19980211, US 1999-247888 19990210; JP 2002507392 W WO 1999-US3020 19990210, JP 2000-531549 19990210; JP 2002507393 W WO 1999-US2944 19990210, JP 2000-531564 19990210; AU 2002027579 A Div ex AU 1999-32910 19990210, AU 2002-27579 20020321; AU 2002027613 A Div ex AU 1999-26741 19990210, AU 2002-27613 20020322; AU 2002027677 A Div ex AU 1999-26742 19990210, AU 2002-27677 20020326; MX 2000007892 A1 MX 2000-7892 20000811; MX 2000007889 A1 WO 1999-US3020 19990210, MX 2000-7889 20000811

FDT AU 9926741 A Based on WO 9941368; EP 1053312 A2 Based on WO 9941368; JP 2002507392 W Based on WO 9941368; JP 2002507393 W Based on WO 9941383; MX 2000007889 A1 Based on WO 9941368

PRAI US 1998-74294P 19980211; US 1998-21769 19980211;
US 1999-247888 19990210; US 1998-105509P 19981023;
AU 2002-27579 20020321; AU 2002-27613 20020322;
AU 2002-27677 20020326

AB WO 9941368 A UPAB: 20031030

NOVELTY - Identification of a polynucleotide (I) that modulates the immune response to a genetic vaccine vector (A), or encodes a polypeptide (II) with similar effect, comprises screening a library of recombinant polynucleotides to identify an optimized (I) having increased modulatory activity compared with non-recombinant polynucleotides from which the library was produced.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for identification of a polynucleotide (Ia) encoding an accessory molecule (IIa) that improves transport and presentation of antigen by a cell.

ACTIVITY - Antibacterial; antiviral; antifungal; anti-allergic; antidiabetic; anti-inflammatory; anti-arthritic; anti-asthma; anticancer; immunomodulatory.

MECHANISM OF ACTION - Induction of a specific immune response.

USE - Optimized (I) are incorporated into (A), or (I) or its encoded (II) are administered together with (A). (A) are used to treat or prevent infections (bacterial, viral or fungal); autoimmune disease (e.g. rheumatoid arthritis, diabetes or multiple sclerosis); other inflammatory conditions (e.g. psoriasis or pancreatitis); immune deficiency; allergy; asthma or cancer (including metastases). (I) are also used for recombinant production of (II).

ADVANTAGE - (I) make it possible to tailor an immune response to particular requirements, e.g. to direct a Th1-type helper response; to increase humoral or cellular responses (functioning as adjuvant); to control B or T cell proliferation; to induce immunogolobulin synthesis or isotype switching.

Dwg.0/15

L8 ANSWER 133 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 68

AN 1999:398304 BIOSIS

DN PREV199900398304

TI **CpG** DNA: A potent signal for growth, activation, and maturation of human dendritic cells.

AU Hartmann, G.; Weiner, G. J.; Krieg, A. M. [Reprint author]

CS Department of Internal Medicine, University of Iowa, 540 EMRB, Iowa City, IA, 52242, USA

SO Proceedings of the National Academy of Sciences of the United States of America, (Aug. 3, 1999) Vol. 96, No. 16, pp. 9305-9310. print.
CODEN: PNASA6. ISSN: 0027-8424.

DT Article

LA English

ED Entered STN: 8 Oct 1999
Last Updated on STN: 8 Oct 1999

AB DNA molecules containing unmethylated **CpG**-dinucleotides in

particular base contexts ("**CpG** motifs") are excellent adjuvants in rodents, but their effects on human cells have been less clear. Dendritic cells (DCs) form the link between the innate and the acquired immune system and may influence the balance between T helper 1 (**Th1**) and **Th2** immune responses. We evaluated the effects of **CpG** oligodeoxynucleotides alone or in combination with granulocyte-macrophage colony-stimulating factor (GMCSF) on different classes of purified human DCs. For primary dendritic precursor cells isolated from human blood, **CpG** oligonucleotides alone were superior to GMCSF in promoting survival and maturation (CD83 expression) as well as expression of class II MHC and the costimulatory molecules CD40, CD54, and CD86 of DCs. Both CD4-positive and CD4-negative peripheral blood dendritic precursor cells responded to **CpG** DNA which synergized with GMCSF but these DCs showed little response to lipopolysaccharide (LPS). In contrast, monocyte-derived DCs did not respond to **CpG**, but they were highly sensitive to LPS, suggesting an inverse correlation between **CpG** and LPS sensitivity in different subsets of DCs. Compared with GMCSF, **CpG** -treated peripheral blood DCs showed enhanced functional activity in the mixed lymphocyte reaction and induced T cells to secrete increased levels of Th1 cytokines. These findings demonstrate the ability of specific **CpG** motifs to strongly activate certain subsets of human DCs to promote Th1-like immune responses, and support the use of **CpG** DNA-based trials for immunotherapy against cancer, allergy, and infectious diseases.

L8 ANSWER 134 OF 159 MEDLINE on STN DUPLICATE 69
AN 1999248218 MEDLINE
DN PubMed ID: 10229876
TI Long term prevention of allergic lung inflammation in a mouse model of asthma by **CpG** oligodeoxynucleotides.
AU Sur S; Wild J S; Choudhury B K; Sur N; Alam R; Klinman D M
CS Division of Allergy and Immunology, Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX 77555, USA.. Sasur@utmb.edu
SO Journal of immunology (Baltimore, Md. : 1950), (1999 May 15) 162 (10) 6284-93.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; AIDS
EM 199906
ED Entered STN: 19990628
Last Updated on STN: 19990628
Entered Medline: 19990614
AB Asthma is an inflammatory disease of the airways that is induced by **Th2** cytokines and inhibited by **Th1** cytokines. Despite a steady increase in the incidence, morbidity, and mortality from asthma, no current treatment can reduce or prevent asthma for a prolonged period. We examined the ability of unmethylated **CpG** oligodeoxynucleotides (ODN), which are potent inducers of Th1 cytokines, to prevent the inflammatory and physiological manifestations of asthma in mice sensitized to ragweed allergen. Administration of **CpG** ODN 48 h before allergen challenge increased the ratio of IFN-gamma to IL-4 secreting cells, diminished allergen-induced eosinophil recruitment, and decreased the number of ragweed allergen-specific IgE-producing cells. These effects of **CpG** ODN were sustained for at least 6 wk after its administration. Furthermore, there was a vigorous Th1 memory response to the recall Ag, inhibition of peribronchial and perivascular lung inflammation, and inhibition of bronchial hyperresponsiveness 6 wk after administration of **CpG** ODN. Administration of **CpG** ODN in IFN-gamma -/- mice failed to inhibit eosinophil recruitment, indicating

a critical role of IFN-gamma in mediating these effects. This is the first report of a treatment that inhibits allergic lung inflammation in presensitized animals for a prolonged period and thus has relevance to the development of an effective long term treatment for asthma.

L8 ANSWER 135 OF 159 MEDLINE on STN DUPLICATE 70
AN 2000040386 MEDLINE
DN PubMed ID: 10570281
TI Phosphorothioate oligodeoxynucleotides promote the in vitro development of human allergen-specific CD4+ T cells into Th1 effectors.
AU Parronchi P; Brugnolo F; Annunziato F; Manuelli C; Sampognaro S; Mavilia C; Romagnani S; Maggi E
CS Department of Internal Medicine, Immunoallergology and Respiratory Disease Unit, University of Florence, Florence, Italy.
SO Journal of immunology (Baltimore, Md. : 1950), (1999 Dec 1) 163 (11) 5946-53.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; AIDS
EM 199912
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991220
AB DNA vaccination is an effective approach in inducing the switch of murine immune responses from a **Th2** to a **Th1** profile of cytokine production that has been related to the activity of unmethylated **CpG** motifs present in bacterial, but not mammalian, DNA. We report here that some synthetic phosphorothioate, but not phosphodiester, oligodeoxynucleotides (ODNs) were able to induce B cell proliferation and to shift the in vitro differentiation of Dermatophagoides pteronyssinus group 1-specific human CD4+ T cells from atopic donors into Th cell effectors showing a prevalent **Th1**, instead of **Th2**, cytokine profile. This latter effect was completely blocked by the neutralization of IL-12 and IFN (alpha and gamma) in bulk culture, suggesting that the Th1-inducing activity of phosphorothioate ODNs was mediated by their ability to stimulate the production of these cytokines by monocytes, dendritic, and NK cells. Cytosine methylation abolished the Th1-inducing activity of ODNs; however, **CpG** dinucleotide-containing ODNs exhibited the Th1-shifting effect independently of the presence or the absence of **CpG** motifs (5'-pur-pur-**CpG** -pyr-pyr-3'). Moreover, the inversion of **CpG** to GpC resulted only in a partial reduction of this activity, suggesting that the motif responsible for the Th1-skewing effect in humans is at least partially different from that previously defined in mice. These results support the concept that the injection of allergens mixed to, or conjugated with, appropriate ODNs may provide a novel allergen-specific immunotherapeutic regimen for the treatment of allergic disorders.

L8 ANSWER 136 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 71
AN 1999:259401 BIOSIS
DN PREV199900259401
TI Gene gun DNA vaccination with Rev-independent synthetic HIV-1 gp160 envelope gene using mammalian codons.
AU Vinner, Lasse; Nielsen, Henrik V.; Bryder, Karin; Corbet, Sylvie; Nielsen, Claus; Fomsgaard, Anders [Reprint author]
CS Department of Virology, Statens Serum Institut, 5 Artillerivej, DK-2300, Copenhagen S, Denmark
SO Vaccine, (April 23, 1999) Vol. 17, No. 17, pp. 2166-2175. print.
CODEN: VACCDE. ISSN: 0264-410X.
DT Article

LA English
ED Entered STN: 2 Jul 1999
Last Updated on STN: 2 Jul 1999
AB DNA immunization with HIV envelope plasmids induce only moderate levels of specific antibodies which may in part be due to limitations in expression influenced by a species-specific and biased HIV codon usage. We compared antibody levels, **Th1/Th2** type and CTL responses induced by synthetic genes encoding membrane bound gp160 versus secreted gp120 using optimized codons and the efficient gene gun immunization method. The in vitro expression of syn.gp160 as gp120 + gp41 was Rev independent and much higher than a classical wt.gp160 plasmid. Mice immunized with syn.gp160 and wt.gp160 generated low and inconsistent ELISA antibody titres whereas the secreted gp120 consistently induced faster seroconversion and higher antibody titres. Due to a higher C + G content the numbers of putative **CpG** immune (Th1) stimulatory motifs were highest in the synthetic gp160 gene. However, both synthetic genes induced an equally strong and more pronounced Th2 response with higher IgG1/IgG2a and IFNgamma/IL-4 ratios than the wt.gp160 gene. As for induction of CTL, synthetic genes induced a somewhat earlier response but did not offer any advantage over wild type genes at a later time point. Thus, optimizing codon usage has the advantage of rendering the structural HIV genes Rev independent. For induction of antibodies the level of expression, while important, seems less critical than optimal contact with antigen presenting cells at locations reached by the secreted gp120 protein. A proposed Th1 adjuvant effect of the higher numbers of **CpG** motifs in the synthetic genes was not seen using gene gun immunization which may be due to the low amount of DNA used.

L8 ANSWER 137 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:101856 CAPLUS
DN 130:266120
TI **CpG** oligodeoxynucleotides can circumvent the Th2 polarization of neonatal responses to vaccines but may fail to fully redirect Th2 responses established by neonatal priming
AU Kovarik, Jiri; Bozzotti, Paola; Love-Homan, Laurie; Pihlgren, Maria; Davis, Heather L.; Lambert, Paul-Henri; Krieg, Arthur M.; Siegrist, Claire-Anne
CS World Health Organization Collaborating Centre for Neonatal Vaccinology, University of Geneva, Geneva, 1211, Switz.
SO Journal of Immunology (1999), 162(3), 1611-1617
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB Neonatal murine responses to a panel of conventional vaccines differ qual. from adult responses by a particular polarization toward a Th2 pattern and a frequent limitation of the Th1 and CTL responses required for protection against intracellular. microorganisms. In contrast, DNA vaccines induce adult-like Th1/CTL neonatal responses against the same vaccine Ags. In this report, we show that this can be related to their content in unmethylated **CpG** motifs. Oligodeoxynucleotides (ODN) containing **CpG** motifs activate neonatal APCs to produce IL-12 in vitro and induce adult-like Th1 responses to tetanus toxoid and measles Ags in vivo, with production of IgG2a-specific Abs and adult-like secretion of IFN-γ and IL-5 by Ag-specific T cells. However, in spite of their capacity to trigger neonatal B cell proliferation in vitro, **CpG**-ODN only partially enhanced early life Ab responses. Finally, using Th1-driving **CpG**-ODN with the boosting dose of a protein vaccine was sufficient to redirect adult but not neonatally primed Th2 responses. These observations could be important for the development of novel vaccines that will have to be effective early in life.
RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 138 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:32813 CAPLUS
DN 132:346552
TI **CpG** oligodeoxynucleotides do not require TH1 cytokines to prevent eosinophilic airway inflammation in a murine model of asthma
AU Kline, Joel N.; Krieg, Arthur M.; Waldschmidt, Thomas J.; Ballas, Zuhair K.; Jain, Vipul; Businga, Thomas R.
CS Departments of Medicine, University of Iowa College of Medicine, Iowa City, IA, 52242, USA
SO Journal of Allergy and Clinical Immunology (1999), 104(6), 1258-1264
CODEN: JACIBY; ISSN: 0091-6749
PB Mosby, Inc.
DT Journal
LA English
AB Oligodeoxynucleotides (ODNs) containing the dinucleotide **CpG** in a specific sequence context (**CpG**-ODNs) have the ability to prevent the development of eosinophilic airway inflammation and bronchial hyperreactivity in a murine model of asthma. The authors have previously demonstrated that **CpG**-ODNs stimulate expression of the TH1-inducing cytokines IFN-γ and IL-12 in a murine model of asthma and that this stimulation is associated with the protection against asthmatic inflammation. The purpose here was to examine whether the protection conferred by **CpG**-ODNs in a schistosome egg-egg antigen murine model of asthma is dependent on the induction of IFN-γ, IL-12, or both. C57BL/6 mice were sensitized to schistosome eggs in the presence or absence of **CpG**-ODNs or control ODNs and then stimulated with soluble egg antigen in the airway. The protection offered by **CpG** -ODNs in these mice was compared with the protection induced by **CpG**-ODNs in IL-12 and IFN-γ knockout mice and in mice treated with anticytokine blocking antibodies. Double-knockout mice (IL-12/IFN-γ) were also generated and used in these studies. Detns. included airway eosinophilic inflammation and bronchial hyperreactivity to inhaled methacholine. The authors found that **CpG**-ODNs confer protection against both airway eosinophilia and bronchial hyperreactivity in the absence of IFN-γ or IL-12 or in the presence of both cytokines together. However, in the absence of either IL-12 or IFN-γ, mice require 10 times as much **CpG**-ODNs to be protected against the induction of airway eosinophilia. The TH2 cytokines IL-4 and IL-5 were reduced in all of the **CpG**-treated mice, although less in the absence of IL-12 and IFN-γ. Thus, **CpG** -ODNs prevent the generation of TH2-like immune responses by multiple mechanisms, which involve, but do not require, IL-12 and IFN-γ. A direct suppressive effect of **CpG**-ODNs on TH2 responses is suggested by their reduction in IFN-γ and IL-12 knockout mice.
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 139 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 72
AN 1999:300763 BIOSIS
DN PREV199900300763
TI Bacterial DNA and **CpG**-containing oligodeoxynucleotides activate cutaneous dendritic cells and induce IL-12 production: Implications for the augmentation of Th1 responses.
AU Jakob, Thilo [Reprint author]; Walker, Patricia S.; Krieg, Arthur M.; von Stebut, Esther; Udey, Mark C.; Vogel, Jonathan C.
CS Klinik und Poliklinik fuer Dermatologie und Allergologie, Technische Universitaet Muenchen, Biedersteiner Strasse 29, D-80802, Muenchen, Germany
SO International Archives of Allergy and Immunology, (Feb.-April, 1999) Vol. 118, No. 2-4, pp. 457-461. print.
CODEN: IAAIEG. ISSN: 1018-2438.

DT Article
LA English
ED Entered STN: 12 Aug 1999
Last Updated on STN: 12 Aug 1999
AB Background: Unmethylated **CpG** sequences in bacterial DNA act as adjuvants selectively inducing Th1 predominant immune responses during genetic vaccination or when used in conjunction with protein Ag. The precise mechanism of this adjuvant effect is unknown. Because dendritic cells (DC) are thought to be crucially involved in T cell priming and **Th1/Th2** education during vaccination via skin, we characterized the effects of bacterial DNA and **CpG**-containing oligodeoxynucleotides (**CpG** ODN) on cutaneous DC. Methods and Results: Stimulation with **CpG** ODN 1826 (6 mug/ml) induced activation of immature Langerhans cell (LC)-like DC as determined by an increased expression of MHC class II and costimulatory molecules, loss of E-cadherin-mediated adhesion and increased ability to stimulate allogeneic T cells. Composition-matched control ODN 1911 lacking **CpG** sequences at equal concentrations was without effect. In comparison to LPS and ODN 1911, **CpG** ODN 1826 selectively stimulated DC to release largeamounts of IL-12 (p40) and little IL-6 or TNF-alpha within 18 h and detectable levels of IL-12 p70 within 72 h. Stimulation with Escherichia coli DNA, but not calf thymus DNA, similarly induced DC maturation and IL-12 p40 production. Injection of **CpG** ODN into murine dermis induced enhanced expression of MHC class II and CD86 by LC in the overlying epidermis and intracytoplasmic IL-12 p40 accumulation in a subpopulation of activated LC. Conclusion: Bacterial DNA and **CpG** ODN stimulate DC in vitro and in vivo and may preferentially elicit Th1-predominant immune responses because they can activate and mobilize DC, inducing them to produce IL-12.

L8 ANSWER 140 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 73
AN 1999:300762 BIOSIS
DN PREV199900300762
TI DNA-based immunization for asthma.
AU Broide, David [Reprint author]; Raz, Eyal
CS University of California San Diego, 9500 Gilman Drive, Basic Science Building, Room 5090, La Jolla, CA, 92093-0635, USA
SO International Archives of Allergy and Immunology, (Feb.-April, 1999) Vol. 118, No. 2-4, pp. 453-456. print.
CODEN: IAAIEG. ISSN: 1018-2438.
DT Article
LA English
ED Entered STN: 12 Aug 1999
Last Updated on STN: 12 Aug 1999
AB Background: Immunostimulatory DNA sequences (**ISS**) containing a **CpG** motif are able to inhibit Th2-mediated airway eosinophilia and bronchial hyperresponsiveness in a mouse model of asthma. Methods: To determine the optimal frequency and timing of intervention with **ISS** in inhibiting Th2 cytokine production and airway eosinophilia, we used **ISS** administration protocols which differed in the frequency (one vs. two doses), route (systemic vs. mucosal) and timing of **ISS** administration (before or together with antigen) in a mouse model of ovalbumin-induced eosinophilic airway inflammation. Results: **ISS** induced Th1 cytokine production (IFN-gamma) and effectively inhibited Th2 cytokine production (IL-5) as well as eosinophilic inflammation when **ISS** was administered before or coadministered with inhaled allergen challenge. Although **ISS** was effective when coadministered with inhaled allergen, it was most effective when administered once 6 days prior to allergen challenge. Mucosal (intranasal and intratracheal) delivery of **ISS** was as effective as systemic (intraperitoneal) **ISS** delivery in inhibiting airway eosinophilia and switching cytokine responses from a **Th2** to a **Th1**

response. Conclusions: **ISS** is most effective in inhibiting airway eosinophilia when administered as a single dose 6 days prior to antigen inhalation. However, **ISS** can also significantly inhibit eosinophilic inflammation, when coadministered with antigen inhalation. Thus, **ISS** administered prior or together with allergen should be considered as a novel method of allergen-based immunotherapy.

L8 ANSWER 141 OF 159 MEDLINE on STN DUPLICATE 74
AN 2000080392 MEDLINE
DN PubMed ID: 10614729
TI Deviation of the allergic IgE to an IgG response by gene immunotherapy.
AU Raz E; Spiegelberg H L
CS Department of Medicine, University of California, San Diego, School of Medicine, La Jolla 92093, USA.
NC AI 37305 (NIAID)
AI 40682 (NIAID)
SO International reviews of immunology, (1999) 18 (3) 271-89. Ref: 49
Journal code: 8712260. ISSN: 0883-0185.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; AIDS
EM 200001
ED Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000124
AB The **Th1/Th2** type immune response to E. coli beta-galactosidase (beta-gal) was compared to that to gene vaccination with plasmid (p) DNA encoding beta-gal. BALB/c mice were immunized with beta-gal in alum or a pDNA construct consisting of a CMV-based promoter and the beta-gal gene (pCMV-LacZ). Beta-gal in alum induced IgG1 and IgE antibodies and the CD4+ T cells from these mice secreted interleukin 4 (IL-4) and IL-5 but no interferon-gamma (IFN-gamma) after in vitro antigen stimulation. In contrast, mice immunized with pCMV-LacZ formed predominantly IgG2a antibodies and their CD4+ T cells secreted IFN-gamma but no IL-4 and IL-5. These data indicate that beta-gal induced a **Th2** and the pCMV-LacZ a **Th1** response to beta-gal. The pDNA induced **Th1** response dominated over the **Th2** response. Mice primed with pCMV-LacZ failed to produce IgE antibodies after a booster injection of beta-gal in alum. Boosting of mice primed with beta-gal in alum with pCMV-LacZ resulted in a 75% decrease in the IgE antibody titer within 6 weeks and IgG2a antibody formation and CD4+ T cells that secreted IFN-gamma in amounts similar to T cells from pDNA primed mice. As shown by adoptive cell transfer, both CD4+ and CD8+ T cells from pDNA immunized mice inhibited an IgE response to beta-gal in alum in the recipient mice. pDNA immunization also inhibited the eosinophilic infiltration of the lung of ovalbumin (OVA) immunized mice after OVA inhalation challenge in an animal model of the late phase reaction. The mechanism of the pDNA induced Th1 immune response was shown to be the result of stimulation by distinct non-coding immunostimulatory DNA sequences (**ISS**) in the backbone of the pDNA. The **ISS** induced antigen presenting cells to secrete cytokines that cause naive T cells to differentiate into Th1 cells (e.g. IFN-alpha, IL-12). The data indicate that gene vaccination induces a Th1 immune response that is capable of down-regulating a preexisting Th2 response and IgE antibody formation. Thus, immunization with pDNA encoding for allergens may provide a novel type of immunotherapy for allergic diseases.

L8 ANSWER 142 OF 159 MEDLINE on STN DUPLICATE 75
AN 1999327276 MEDLINE
DN PubMed ID: 10399077

TI Phagocytic antigen processing and effects of microbial products on antigen processing and T-cell responses.
AU Ramachandra L; Chu R S; Askew D; Noss E H; Canaday D H; Potter N S; Johnsen A; Krieg A M; Nedrud J G; Boom W H; Harding C V
CS Institute of Pathology, Case Western Reserve University, Cleveland, Ohio 44106, USA.
NC AI34343 (NIAID)
AI35726 (NIAID)
CA70149 (NCI)
+
SO Immunological reviews, (1999 Apr) 168 217-39. Ref: 188
Journal code: 7702118. ISSN: 0105-2896.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199909
ED Entered STN: 19990925
Last Updated on STN: 19990925
Entered Medline: 19990914
AB Processing of exogenous antigens and microbes involves contributions by multiple different endocytic and phagocytic compartments. During the processing of soluble antigens, different endocytic compartments have been demonstrated to use distinct antigen-processing mechanisms and to process distinct sets of antigenic epitopes. Processing of particulate and microbial antigens involves phagocytosis and functions contributed by phagocytic compartments. Recent data from our laboratory demonstrate that phagosomes containing antigen-conjugated latex beads are fully competent class II MHC (MHC-II) antigen-processing organelles, which generate peptide:MHC-II complexes. In addition, phagocytosed antigen enters an alternate class I MHC (MHC-I) processing pathway that results in loading of peptides derived from exogenous antigens onto MHC-I molecules, in contrast to the cytosolic antigen source utilized by the conventional MHC-I antigen-processing pathway. Antigen processing and other immune response mechanisms may be activated or inhibited by microbial components to the benefit of either the host or the pathogen. For example, antigen processing and T-cell responses (e.g. **Th1** vs **Th2** differentiation) are modulated by multiple distinct microbial components, including lipopolysaccharide, cholera toxin, heat labile enterotoxin of Escherichia coli, DNA containing **CpG** motifs (found in prokaryotic and invertebrate DNA but not mammalian DNA) and components of Mycobacterium tuberculosis.

L8 ANSWER 143 OF 159 EMBASE on STN
AN 2000008608 EMBASE
TI Effects of **CpG** DNA on **Th1/Th2** balance in asthma.
AU Kline J.N.
CS J.N. Kline, Division of Pulmonary Medicine, University of Iowa, College of Medicine, 200 Newton Drive, Iowa City, IA 52242, United States. joel-kline@uiowa.edu
SO Current Topics in Microbiology and Immunology, (1999) 247/- (211-225). Refs: 52
ISSN: 0070-217X CODEN: CTMIA3
CY Germany
DT Journal; General Review
FS 015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
LA English
SL English

AB Thus, in our studies, we demonstrated that **CpG** ODN are effective in preventing the development of eosinophilic airway inflammation and bronchial hyper-reactivity in a murine model of asthma. Antigen-associated elevation of serum IgE levels is also suppressed. **CpG** ODN, administered in conjunction with antigen, is also effective in down-regulation of established Th2 responses. This protection is neither murine strain-dependent nor model- dependent. Although these effects of **CpG** ODN are associated with the induction of the Th1 cytokines IFN-γ and IL-12, neither cytokine is absolutely required for the protection. These results suggest that **CpG** ODN may be an effective immunomodulatory agent in the treatment, and possibly prevention, of asthma.

L8 ANSWER 144 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 76
AN 1999:528342 BIOSIS
DN PREV199900528342
TI Plasmid DNA vaccines are effective in the absence of IFNgamma.
AU Hassett, Daniel E.; Zhang, Jie; Whitton, J. Lindsay [Reprint author]
CS Department of Neuropharmacology, CVN-9, Scripps Research Institute, 10550 N. Torrey Pines Rd., La Jolla, CA, 92037, USA
SO Virology, (Oct. 10, 1999) Vol. 263, No. 1, pp. 175-183. print.
CODEN: VIRLAX. ISSN: 0042-6822.
DT Article
LA English
ED Entered STN: 10 Dec 1999
Last Updated on STN: 10 Dec 1999
AB Intramuscular injection of bacterially derived plasmid DNA results in the development of both humoral and cellular immune responses against plasmid-encoded antigens. Immunostimulatory **CpG** sequences within bacterial DNA are thought to enhance this process by stimulating the secretion of proinflammatory cytokines such as interferon gamma (IFNgamma) by cells of the innate immune system. Although IFNgamma induction by **CpG** elements within plasmid DNA has been documented in vitro and more recently in vivo, and coimmunization with plasmids expressing IFNgamma has been shown to enhance DNA-immunization-induced immune responses, it is unclear if IFNgamma is necessary for successful DNA immunization. To address this issue, we compared humoral and cellular immune responses in wild-type and IFNgamma-deficient mice vaccinated with a plasmid (pCMVNP) expressing the nucleoprotein gene from the arenavirus lymphocytic choriomeningitis virus (LCMV). IFNgamma-positive (BALB/c) and IFNgamma-negative (GKO) mice responded to DNA vaccination by the development of antigen-specific CD8+ T cells, which were detectable directly ex vivo by intracellular cytokine staining and comprised 0.7-2.5% of all CD8+ T cells in the vaccinee. DNA vaccines also induced virus-specific cytotoxic T lymphocytes (CTL), even in the absence of IFNgamma. DNA vaccination of both mouse strains also was associated with a significant reduction in viral titers after LCMV challenge, indicating that, at least in the presence of other immune effector mechanisms, IFNgamma is not required for induction of protective anti-viral immunity by DNA immunization. No quantitative differences were observed in antiviral IgG levels among GKO and BALB/c vaccinees, although GKO mice did exhibit a significant reduction of the IgG2a:IgG1 ratio, in agreement with the previously documented requirement for IFNgamma in isotype switching to IgG2a. Immunized BALB/c mice produced similar levels of both IgG1 and IgG2a, indicating a mixed **Th1/Th2** response to intramuscular immunization with pCMVNP. These results show that IFNgamma induction by bacterially derived plasmid DNA does not contribute to the magnitude of the antibody response and is not required for the induction or short-term maintenance of DNA-induced CTL. However, IFNgamma is necessary for the development of IgG2a antibodies that may be crucial for protection against some pathogens.

L8 ANSWER 145 OF 159 MEDLINE on STN
AN 1999193078 MEDLINE
DN PubMed ID: 10093118
TI Inhibition of allergic inflammation in the lung by plasmid DNA allergen immunization.
AU Spiegelberg H L; Broide D; Tighe H; Roman M; Raz E
CS Department of Pediatrics, University of California San Diego, School of Medicine, La Jolla 92093-0833, USA.. hansspiege@aol.com
NC AI 40682 (NIAID)
SO Pediatric pulmonology. Supplement, (1999) 18 118-21.
Journal code: 9014095. ISSN: 1054-187X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199905
ED Entered STN: 19990607
Last Updated on STN: 19990607
Entered Medline: 19990525
AB The nature of the immune response (**Th1/Th2**) in mice to protein antigens or allergens was compared to that of immunization with pDNA encoding the same antigens. pDNA immunization induced a Th1 response and no IgE antibodies whereas the proteins induced a Th2 response and IgE antibodies. Furthermore, the pDNA induced Th1 response dominated over the protein elicited Th2 response in a secondary immune response. In particular, a preexisting Th2 response (as is the case in allergic patients) did not prevent a new Th1 response to an allergen-pDNA booster injection. The major reason why pDNA immunization induced a Th1 response to allergens was the presence of immunostimulatory non-coding DNA sequences (**ISS**) in the plasmid constructs having a **CpG** motif. These **ISS** caused antigen presenting cells to secrete INF-alpha, INF-beta and IL-12, all cytokines that induce naive T cells to differentiate into CD4+ Th1 cells and CD8+ Tc1 cells. Passive transfer of both Th1 and Tc1 cells from pDNA immunized mice into naive mice inhibited a Th2 response and IgE antibody formation to a subsequent injection of allergen in alum. pDNA immunization or **ISS**-oligonucleotide injection prior to allergen challenge reduced both immediate type airway sensitivity and late phase allergen induced eosinophil filtration of the lung. Allergen-pDNA immunization may provide a novel type of immunotherapy for the treatment of allergic diseases in man. Since only small amounts of allergen are secreted by the allergen-pDNA transformed cells, allergen-pDNA immunotherapy will unlikely carry the risk of the anaphylactic reactions that are associated with classical allergen injection immunotherapy.

L8 ANSWER 146 OF 159 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 1999107639 EMBASE
TI Inhibition of allergic inflammation in the lung by plasmid DNA allergen immunization.
AU Spiegelberg H.L.; Broide D.; Tighe H.; Roman M.; Raz E.
CS Dr. H.L. Spiegelberg, Div. of Pediatric Immunology/Allergy, Department of Pediatrics 0833, UCSD School of Medicine, San Diego, CA 92093-0833, United States. hansspiege@aol.com
SO Pediatric Pulmonology, (1999) 27/SUPPL. 18 (118-121).
Refs: 15
ISSN: 8755-6863 CODEN: PEPUES
CY United States
DT Journal; Conference Article
FS 007 Pediatrics and Pediatric Surgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English

SL English

AB The nature of the immune response (**Th1/Th2**) in mice to protein antigens or allergens was compared to that of immunization with pDNA encoding the same antigens. pDNA immunization induced a Th1 response and no IgE antibodies whereas the proteins induced a Th2 response and IgE antibodies. Furthermore, the pDNA induced Th1 response dominated over the protein elicited Th2 response in a secondary immune response. In particular, a preexisting Th2 response (as is the case in allergic patients) did not prevent a new Th1 response to an allergen-pDNA booster injection. The major reason why pDNA immunization induced a Th1 response to allergens was the presence of immunostimulatory non-coding DNA sequences (**ISS**) in the plasmid constructs having a **CpG** motif. These **ISS** caused antigen presenting cells to secrete INF-α, INF-β and IL-12, all cytokines that induce naive T cells to differentiate into CD4+ Th1 cells and CD8+ Tc1 cells. Passive transfer of both Th1 and Tc1 cells from pDNA immunized mice into naive mice inhibited a Th2 response and IgE antibody formation to a subsequent injection of allergen in alum. pDNA immunization or **ISS**-oligonucleotide injection prior to allergen challenge reduced both immediate type airway sensitivity and late phase allergen induced eosinophil infiltration of the lung. Allergen-pDNA immunization may provide a novel type of immunotherapy for the treatment of allergic diseases in man. Since only small amounts of allergen are secreted by the allergen-pDNA transformed cells, allergen-pDNA immunotherapy will unlikely carry the risk of the anaphylactic reactions that are associated with classical allergen injection immunotherapy.

L8 ANSWER 147 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 77

AN 1998-520792 [44] WPIDS

DNC C1998-156334

TI Use of oligonucleotides containing an unmethylated **CpG** dinucleotide - useful as, e.g. adjuvant with antigen, or nucleic acid encoding antigen for inducing immune response in subject.

DC B04 D16

IN DAVIS, H L; KRIEG, A M; SCHORR, J

PA (OTTA-N) OTTAWA CIVIC LOEB RES INST; (QIAG-N) QIAGEN GMBH; (IOWA) UNIV IOWA RES FOUND; (LOEB-N) LOEB HEALTH RES INST AT OTTAWA HOSPITAL; (COLE-N) COLEY PHARM GMBH; (CPGI-N) CPG IMMUNOPHARMACEUTICALS GMBH; (OTTA-N) OTTAWA HEALTH RES INST

CYC 80

PI WO 9840100 A1 19980917 (199844)* EN 67
RW: AT BE CH DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9867595 A 19980929 (199906)
EP 1005368 A1 20000607 (200032) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2002511841 W 20020416 (200242) 54
US 6406705 B1 20020618 (200244)
US 2002164341 A1 20021107 (200275)
AU 753688 B 20021024 (200277)
US 2003091599 A1 20030515 (200335)
US 2003224010 A1 20031204 (200380)

ADT WO 9840100 A1 WO 1998-US4703 19980310; AU 9867595 A AU 1998-67595 19980310; EP 1005368 A1 EP 1998-912919 19980310, WO 1998-US4703 19980310; JP 2002511841 W JP 1998-539730 19980310, WO 1998-US4703 19980310; US 6406705 B1 Provisional US 1997-40376P 19970310, CIP of WO 1998-US4703 19980310, CIP of US 1998-154614 19980916, US 1999-325193 19990603; US 2002164341 A1 Provisional US 1997-40376P 19970310, CIP of WO 1998-US4703

19980310, CIP of US 1998-154614 19980916, Div ex US 1999-325193 19990603, US 2001-23909 20011218; AU 753688 B AU 1998-67595 19980310; US 2003091599 A1 Provisional US 1997-40376P 19970310, CIP of WO 1998-US4703 19980310, CIP of US 1998-154614 19980916, Div ex US 1999-325193 19990603, Cont of US 2001-23909 20011218, US 2002-300247 20021120; US 2003224010 A1 Provisional US 1997-40376P 19970310, CIP of WO 1998-US4703 19980310, CIP of US 1998-154614 19980916, Div ex US 1999-325193 19990603, Cont of US 2001-23909 20011218, US 2003-434696 20030509

FDT AU 9867595 A Based on WO 9840100; EP 1005368 A1 Based on WO 9840100; JP 2002511841 W Based on WO 9840100; AU 753688 B Previous Publ. AU 9867595, Based on WO 9840100; US 2003091599 A1 Div ex US 6406705; US 2003224010 A1 Div ex US 6406705

PRAI US 1997-40376P 19970310; US 1998-154614 19980916;
US 1999-325193 19990603; US 2001-23909 20011218;
US 2002-300247 20021120; US 2003-434696 20030509

AB WO 9840100 A UPAB: 20020823
The following are claimed: (1) a method for inducing protective immune response in a subject having or at risk of having infection with an infectious organism, comprising administering to the subject an antigen and an oligonucleotide (ON) containing at least 1 unmethylated **CpG** dinucleotide; (2) a method similar to (1) comprising administering a nucleic acid encoding an antigenic polypeptide and ON as in (1), or optionally an antigen; (3) a method of treating a subject having an infectious disorder that is chronic or likely to become chronic, comprising administering an antigen and ON, and/or optionally a nuclec acid as in (2), and (4) a therapeutic composition comprising an antigen and ON containing an immunostimulatory **CpG** motif in a carrier, and optionally a nucleic acid encoding an antihgenic protein.
USE - ONs containing at least 1 unmethylated **CpG** dinucleotide affect the immune response in a subject by activating natural killer cells (NK) or redirecting a subject's immune response from a **Th2** to a **Th1** response by inducing monocytic and other cells to produce Th1 cytokines. These nucleic acids containing at least 1 unmethylated **CpG** can be used as an adjuvant, specifically to induce an immune response against an antigenic protein, and are used particularly for virally mediated disorders, e.g. hepatitis B virus infection.
Dwg.0/11

L8 ANSWER 148 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1999-080827 [07] WPIDS
CR 1999-059898 [05]; 2003-895228 [82]; 2004-081744 [08]
DNC C1999-024197
TI New oligonucleotide that inhibits action of immunostimulatory sequence oligonucleotides - particularly those present in gene therapy vectors or microbial pathogens, used to prolong gene therapy expression and to treat e.g. infections or autoimmune disease.
DC B04 D16
IN RAY, E; ROMAN, M; RAZ, E
PA (DYNA-N) DYNAVAX TECHNOLOGIES CORP; (REGC) UNIV CALIFORNIA; (RAZE-I) RAZ E; (ROMA-I) ROMAN M
CYC 83
PI WO 9855609 A1 19981210 (199907)* EN 49
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
AU 9878113 A 19981221 (199919)
EP 1003850 A1 20000531 (200031) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 6225292 B1 20010501 (200126)

JP 2002505580 W 20020219 (200216) 44
US 2002086839 A1 20020704 (200247)
AU 755322 B 20021212 (200305)
ADT WO 9855609 A1 WO 1998-US11391 19980605; AU 9878113 A AU 1998-78113 19980605; EP 1003850 A1 EP 1998-926229 19980605, WO 1998-US11391 19980605; US 6225292 B1 Provisional US 1997-48793P 19970606, US 1998-92314 19980605; JP 2002505580 W WO 1998-US11391 19980605, JP 1999-502803 19980605; US 2002086839 A1 Provisional US 1997-48793P 19970606, Cont of US 1998-92314 19980605, US 2001-770943 20010125; AU 755322 B AU 1998-78113 19980605
FDT AU 9878113 A Based on WO 9855609; EP 1003850 A1 Based on WO 9855609; JP 2002505580 W Based on WO 9855609; US 2002086839 A1 Cont of US 6225292; AU 755322 B Previous Publ. AU 9878113, Based on WO 9855609
PRAI US 1997-48793P 19970606; US 1998-92314 19980605;
US 2001-770943 20010125
AB WO 9855609 A UPAB: 20040202
Oligonucleotide (I) having a hexamer region of sequence 5'-Pu-Pu-Y-Z-Py-Py or 5'-Pu-Pu-Y-Z-Py-polyPy for inhibiting immunostimulation caused by immunostimulating-sequence oligonucleotides (II) that contain a hexamer region consisting of at least one **CpG** motif flanked by two 5'-Pu and two 3'-Py is new. Pu = purine; Py = pyrimidine; Y = any natural or synthetic nucleotide other than C; Z = any natural or synthetic nucleotide, but is Y is not Guanosine (G) or Inosine (I), then Z must be. Also new are methods for identifying (I) and for detecting (II) in a host cell.

USE - (I) are used to inhibit immunostimulatory activity of (II) when this is present in (i) a recombinant expression vector (being used for gene therapy or genetic immunisation) or (ii) a microbe (particularly one in a host and associated with an autoimmune disease). Particularly (I) prolong gene expression from the vector and reduce inflammation caused by microbial infection. They also modulate activity of (II), e.g. where these are used as adjuvants to boost an immune response, e.g. in immunotherapy, in contact with vertebrate lymphocytes or monocytes by reducing the **Th1**-type response and stimulating the **Th2**-type response to an antigen (including antigen-stimulated immunoglobulin (Ig) G1 production).

ADVANTAGE - Prolonged expression from the gene therapy vector avoids the need for repeated treatments and re-engineering of the vector to eliminate (II). (I) provide precise control over the effect of (II)-based adjuvants and can be used even where the existence, identity and location of (II) are unknown. (I) are effective at very low doses.
Dwg.5/5

L8 ANSWER 149 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1998-480941 [41] WPIDS
DNC C1998-145520
TI Use of nucleic acids containing an unmethylated **CpG** - for treating a subject having or at risk of having an acute decrement in air flow or inhibiting an inflammatory response.
DC B04 D16
IN KRIEG, A M; SCHWARTZ, D A
PA (IOWA) UNIV IOWA RES FOUND
CYC 22
PI WO 9837919 A1 19980903 (199841)* EN 65
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 9866674 A 19980918 (199908)
EP 1039935 A1 20001004 (200050) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 6214806 B1 20010410 (200122)
AU 738513 B 20010920 (200164)
JP 2001513776 W 20010904 (200165) 61
ADT WO 9837919 A1 WO 1998-US3678 19980225; AU 9866674 A AU 1998-66674 19980225; EP 1039935 A1 EP 1998-908714 19980225, WO 1998-US3678 19980225;

US 6214806 B1 Provisional US 1997-39405P 19970228, US 1998-30701 19980225; AU 738513 B AU 1998-66674 19980225; JP 2001513776 W JP 1998-537810 19980225, WO 1998-US3678 19980225

FDT AU 9866674 A Based on WO 9837919; EP 1039935 A1 Based on WO 9837919; AU 738513 B Previous Publ. AU 9866674, Based on WO 9837919; JP 2001513776 W Based on WO 9837919

PRAI US 1997-39405P 19970228; US 1998-30701 19980225

AB WO 9837919 A UPAB: 19981014

A method for treating a subject having, or at risk of having an acute decrement in air flow, comprising administering a nucleic acid sequence containing at least one unmethylated **CpG**.

Also claimed are: (1) a method of inhibiting an inflammatory response in a subject having inhaled or at risk of inhaling lipopolysaccharide (LPS), comprising administering a nucleic acid sequence containing at least one unmethylated **CpG**; (2) a method of modifying the level of a cytokine in a subject having inhaled or at risk of inhaling LPS, comprising administering a nucleic acid sequence containing at least one unmethylated **CpG** dinucleotide; (3) an isolated nucleic acid sequence comprising at least one unmethylated **CpG** dinucleotide having a sequence as selected from: ATAATCGACGTTCAAGCAAG; ATAATAGAGCTTCAAGCAAG; CGCGCGCGCGCGCGCGCGCG; TCTCCCAGCGAGCGCCAT; ATAATCCAGCTTGAACCAAG; TCCATGACGTTCCTGACGTT; GGGGTCAACGTTGAGGGGGG; GCGGCGGGCGGCGCGCGCCC; GGGGTCTGTGCTTTTGGGGGG; GGCGGCGGCGGCGGCGGCGG.

USE - The nucleic acid containing an unmethylated **CpG** dinucleotide affect an immune response in a subject by activating natural killer cells (NK) or redirecting a subject's immune response from a **Th2** to a **Th1** response by inducing monocytic and other cells to produce Th1 cytokines. They can be used to treat pulmonary disorders having an immunologic component, such as asthma or environmentally induced airway disease. They can also be used to treat diseases associated with Gram-positive bacterial infections or endotoxemia including bacterial meningitis, neonatal sepsis, cystic fibrosis, inflammatory bowel disease and liver cirrhosis, Gram-negative pneumonia, Gram-negative abdominal abscess, haemorrhagic shock, disseminated intravascular coagulation, or an inflammatory response to LPS.

Dwg.0/14

L8 ANSWER 150 OF 159 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

AN 1998-272127 [24] WPIDS

CR 1996-105847 [11]; 2000-086224 [07]; 2001-217934 [22]; 2001-280761 [29]; 2001-380456 [40]; 2002-689667 [74]; 2003-466135 [44]; 2003-512356 [48]; 2003-708674 [67]; 2003-831664 [77]; 2004-088215 [09]; 2004-356245 [33]; 2004-374746 [35]

DNC C1998-084968

TI New **immunostimulatory nucleic acid** molecules - which contain at least one unmethylated **CpG** dinucleotide, used for treating e.g. tumours, infections or autoimmune disease.

DC B04 D16

IN KLINE, J N; KLINMAN, D; KRIEG, A M; STEINBERG, A D; WEINER, G; STEINBERG, A; KLINE, J

PA (IOWA) UNIV IOWA RES FOUND; (USSH) US DEPT HEALTH & HUMAN SERVICES; (KLIN-I) KLINE J; (KLIN-I) KLINMAN D; (KRIE-I) KRIEG A M; (STEI-I) STEINBERG A D

CYC 79

PI WO 9818810 A1 19980507 (199824)* EN 109

RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW

AU 9852424 A 19980522 (199840)

EP 948510 A1 19991013 (199947) EN

R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
CN 1235609 A 19991117 (200013)
NZ 335397 A 20001124 (200065)
JP 2001503267 W 20010313 (200117) 110
KR 2000052994 A 20000825 (200121)
AU 2001097249 A 20020207 (200219)#
US 2003050261 A1 20030313 (200321)
JP 2003286174 A 20031007 (200367) 55
JP 2004041224 A 20040212 (200413) 66

ADT WO 9818810 A1 WO 1997-US19791 19971030; AU 9852424 A AU 1998-52424 19971030; EP 948510 A1 EP 1997-947311 19971030, WO 1997-US19791 19971030; CN 1235609 A CN 1997-199352 19971030; NZ 335397 A NZ 1997-335397 19971030, WO 1997-US19791 19971030; JP 2001503267 W WO 1997-US19791 19971030, JP 1998-520784 19971030; KR 2000052994 A WO 1997-US19791 19971030, KR 1999-703873 19990430; AU 2001097249 A Div ex AU 1998-52424 19971030, AU 2001-97249 20011214; US 2003050261 A1 CIP of US 1994-276358 19940715, CIP of US 1995-386063 19950207, Div ex US 1996-738652 19961030, US 2001-818918 20010327; JP 2003286174 A Div ex JP 1998-520784 19971030, JP 2003-56446 19971030; JP 2004041224 A Div ex JP 1998-520784 19971030, JP 2003-319045 20030910

FDT AU 9852424 A Based on WO 9818810; EP 948510 A1 Based on WO 9818810; NZ 335397 A Based on WO 9818810; JP 2001503267 W Based on WO 9818810; KR 2000052994 A Based on WO 9818810; US 2003050261 A1 CIP of US 6194388, Div ex US 6207646

PRAI US 1996-738652 19961030; AU 2001-97249 20011214;
US 1994-276358 19940715; US 1995-386063 19950207;
US 2001-818918 20010327

AB WO 9818810 A UPAB: 20040603

An isolated nucleic acid (NA) sequence (A) which contains at least one unmethylated **CpG** dinucleotide, having formula (I):

5' N1X1CGX2N2 3' (I);

where at least one nucleotide separates consecutive CpGs; X1 is adenine, guanine, or thymine; X2 is cytosine or thymine; N is any nucleotide and N1 + N2 is 0-26 bases with the provisoin that N1 and N2 does not contain a CCGG tetramer or more than one CCG or CGG trimer; and the NA sequence is 8-30 bases in length.

Also claimed are: (1) an isolated NA sequence containing at least one unmethylated **CpG** dinucleotide and having formula (II):

5' NX1X2CGX3X4N 3' (II);

where at least one nucleotide separates consecutive CpGs; X1 and X2 are selected from GpT, GpG, GpA, ApT and ApA; X3and X4 are selected from TpT or CpT; N is any nucleotide and N1 + N2 is 0-26 bases with the provision that N1 and N2 does not contain a CCGG tetramer or more than one CCG or CGG trimer; and the NA sequence is 8-30 bases in length; and (2) a method for treating a subject having an autoimmune or other **CpG** associated disorder by inhibiting **CpG**-mediated leukocyte activation, comprising administering to the subject an inhibitor of endosomal acidification, in a carrier.

USE - The nucleic acids activate lymphocytes in a subject and redirect a subject's immune response from a **Th2** to a **Th1** (e.g. by inducing monocytic cells and other cells to produce Th1 cytokines, including IL-12, IFN-gamma and GM-CSF). By redirecting a subject's immune response from **TH2** to **Th1**, products can be used to treat or prevent an asthmatic disorder. In addition, the products can be administered to a subject in conjunction with a particular allergen as a type of desensitisation therapy to treat or prevent the occurrence of an allergic reaction associated with an asthmatic disorder. They can be used as an artificial adjuvant during antibody generation in a mammal such as a mouse or a human. They can also be used to treat immune system deficiencies. They can be used to treat disorders such as tumours or a viral, fungal, bacterial or parasitic infection. The NA (A) or as described in (1) can be used to stimulate cytokine production especially IL-12, IL-6, IFN-g, TNF- alpha , and GM-CSF or may be used to stimulate

NK lytic activity or B cell proliferation in humans(all claimed). (A) or the NA as in (1) may also be used to treat asthamatic disorder or may be used as an adjuvant (all claimed). Autoimmune diseases or other **CpG** associatted disorders can be treated by inhibbitting **CpG** mediatted leukocyte activation using inhibitors of endosomal acidification e.g. to treat disorders such as systemic lupus erythematosus, sepsis, inflammatory bowel disease, psoriasis, gingivitis, arthritis, Crohn's disease, Grave's disease or asthma (all claimed). Dwg.0/15

L8 ANSWER 151 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 78
AN 1999:58917 BIOSIS
DN PREV199900058917
TI **CpG** DNA can induce strong Th1 humoral and cell-mediated immune responses against hepatitis B surface antigen in young mice.
AU Millan, Cynthia L. Brazolot; Weeratna, Risini; Krieg, Arthur M.; Siegrist, Claire-Anne; Davis, Heather L. [Reprint author]
CS Loeb Res. Inst., 725 Parkdale Ave., Ottawa, ON K1Y 4E9, Canada
SO Proceedings of the National Academy of Sciences of the United States of America, (Dec. 22, 1998) Vol. 95, No. 26, pp. 15553-15558. print.
CODEN: PNASA6. ISSN: 0027-8424.
DT Article
LA English
ED Entered STN: 16 Feb 1999
Last Updated on STN: 16 Feb 1999
AB Successful neonatal immunization of humans has proven difficult. We have evaluated **CpG**-containing oligonucleotides as an adjuvant for immunization of young mice (1-14 days old) against hepatitis B virus surface antigen. The protein-alum-**CpG** formulation, like the DNA vaccine, produced seroconversion of the majority of mice immunized at 3 or 7 days of age, compared with 0-10% with the protein-alum or protein-**CpG** formulations. All animals, from neonates to adults, immunized with the protein-alum vaccine exhibited strong T helper (Th) 2-like responses (predominantly IgG1, weak or absent cytotoxic T lymphocytes (CTL)). Th2-type responses also were induced in young mice with protein-**CpG** (in 1-, 3-, and 7-day-old mice) and protein-alum-**CpG** (in 1- and 3-day-old mice) but immunization carried out at older ages gave mixed **Th1/Th2** (Th0) responses. DNA vaccines gave Th0-like responses when administered at 1 and 7 days of age and Th1-like (predominantly IgG2a and CTL) responses with 14-day-old or adult mice. Surprisingly, the protein-alum-**CpG** formulation was better than the DNA vaccine for percentage of seroconversion, speed of appearance, and peak titer of the antibody response, as well as prevalence and strength of CTL. These findings may have important implications for immunization of human infants.

L8 ANSWER 152 OF 159 MEDLINE on STN DUPLICATE 79
AN 1998217143 MEDLINE
DN PubMed ID: 9558060
TI **CpG** oligodeoxynucleotides trigger protective and curative Th1 responses in lethal murine leishmaniasis.
AU Zimmermann S; Egeter O; Hausmann S; Lipford G B; Rocken M; Wagner H; Heeg K
CS Institute of Medical Microbiology, Immunology and Hygiene, Technische Universitat Munchen, Germany.
SO Journal of immunology (Baltimore, Md. : 1950), (1998 Apr 15) 160 (8) 3627-30.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; AIDS

EM 199805
ED Entered STN: 19980514
Last Updated on STN: 19980514
Entered Medline: 19980504
AB Synthetic oligodeoxynucleotides containing **CpG** dinucleotides (**CpG**-ODN) mimic the immunostimulatory qualities of bacterial DNA. We asked whether immunostimulation by **CpG**-ODN predisposes for a commitment toward a **Th1** vs a **Th2** response in Leishmania major infection, a model for a lethal Th2-driven disease, in BALB/c mice. **CpG**-ODN induced Th1 effector T cells in vitro and conveyed protective immunity to disease-prone BALB/c mice in vivo. Conversion to a Th1-driven resistant phenotype was associated with IL-12 production and maintained the expression of IL-12R beta2-chains. Most strikingly, **CpG**-ODN were even curative when given as late as 20 days after lethal L. major infection, indicating that **CpG**-ODN revert an established Th2 response. These findings imply an important role of bacterial DNA and **CpG**-ODN in the instruction of adaptive immune responses. They also point to the therapeutic potential of **CpG**-ODN in redirecting curative **Th1** responses in **Th2**-driven disorders.

L8 ANSWER 153 OF 159 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:659951 CAPLUS
DN 130:23793
TI Novel approaches for the induction of T helper 1 (**Th1**)- or **Th2**-type mucosal and parenteral immune responses
AU Marinaro, Mariarosaria; Boyaka, Prosper N.; Kiyono, Hiroshi; McGhee, Jerry R.
CS Immunobiology Vaccine Center, Departments of Microbiology and Oral Biology, The University of Alabama at Birmingham, Birmingham, 35294, USA
SO Expert Opinion on Investigational Drugs (1998), 7(10), 1657-1666
CODEN: EOIDER; ISSN: 1354-3784
PB Ashley Publications
DT Journal; General Review
LA English
AB A review with 66 refs. Mucosal surfaces are constantly challenged by micro-organisms and are protected by an integrated component of the immune system called mucosa-associated lymphoreticular tissue (MALT). The immune responses elicited at the mucosal level are regulated by T-helper (Th) cells and involve secretory IgA (S-IgA) antibodies (Abs) and cytotoxic T-lymphocytes (CTLs). Mucosal immunization has the advantage over parenteral immunization, of inducing S-IgA Abs and of conferring protection at both the mucosal and parenteral levels; however, administration of soluble antigens through a mucosal route very seldom results in significant mucosal and systemic immune responses. Therefore, appropriate mucosal adjuvants, recombinant bacterial and viral vectors and delivery systems have been developed to increase the immunogenicity of vaccine antigens and to preferentially induce antigen-specific T-helper (Th)1- or Th2-type responses, which in turn result in polarized effector immune responses. Understanding the mechanisms underlying **Th1**- and **Th2**-type developmental pathways and the ability of novel mucosal adjuvants and delivery systems to target the desired **Th1** - or **Th2**-type immune response would help to design effective mucosal vaccines, inducing predominant cell-mediated or humoral responses.
RE.CNT 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 154 OF 159 MEDLINE on STN
AN 1999096294 MEDLINE
DN PubMed ID: 9881967
TI Modulation of chromatin structure regulates cytokine gene expression during T cell differentiation.
AU Agarwal S; Rao A

CS Department of Pathology, Harvard Medical School, Center for Blood Research, Boston, Massachusetts 02115, USA.. arao@cbr.med.harvard.edu
NC P01 AI35297 (NIAID)
R01 CA42471 (NCI)
SO Immunity, (1998 Dec) 9 (6) 765-75.
Journal code: 9432918. ISSN: 1074-7613.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199901
ED Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990128
AB Differentiating cells undergo programmed alterations in their patterns of gene expression, which are often regulated by structural changes in chromatin. Here we demonstrate that T cell differentiation results in long-range changes in the chromatin structure of effector cytokine genes, which persist in resting **Th1** and **Th2** cells in the absence of further stimulation. Differentiation of naive T helper cells into mature Th2 cells is associated with chromatin remodeling of the IL-4 and IL-13 genes, whereas differentiation into Th1 cells evokes remodeling of the IFNgamma but not IL-4 or IL-13 genes. IL-4 locus remodeling is accompanied by demethylation and requires both antigen stimulation and STAT6 activation. We propose that chromatin remodeling of cytokine gene loci is functionally associated with productive T cell differentiation and may explain the coordinate regulation of Th2 cytokine genes.

L8 ANSWER 155 OF 159 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
AN 1999-12698 BIOTECHDS
TI DNA immunotherapeutics: new potential treatment modalities for allergic disease;
nucleic acid vaccine for allergy gene therapy; a review
AU Goodman J S; *van Uden J H; Kobayashi H; Broide D; Raz E
CS Univ.California
LO Department of Medicine, University of California School of Medicine, 9500 Gilman Drive, La Jolla, CA 92093-0663, USA.
Email: jvanuden@ucsd.edu
SO Int.Arch.Allergy Immunol.; (1998) 116, 3, 177-87
CODEN: IAAIEG ISSN: 1018-2438
DT Journal
LA English
AB Genetic immunization with nucleic acid vaccines is a relatively new approach to vaccination, one that has generated considerable interest for its potential to prevent or treat a number of types of disease processes. Initially work into this area focused on its potential applications in infectious disease, but it was soon recognized that the antigen-specific Th1 response typically generated by genetic immunization protocols could be also be useful for the treatment of allergic disease. This review specifically covers the following areas: overview of gene vaccines; gene vaccines induce an antigen-specific Th1 primary response; gene vaccines inhibit the induction of a secondary Th2 response; genetic vaccination induces a switch from a primary **Th2** to a secondary **Th1** response; genetic vaccination inhibits pulmonary eosinophilia; immunostimulatory DNA sequences; **ISS** elicit a Th1-inducing cytokine milieu; protein/**ISS** coinjection inhibits pulmonary eosinophilia; and DNA immunotherapeutics - a possible alternative to immunotherapy. (75 ref)

L8 ANSWER 156 OF 159 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 1998215509 EMBASE
TI Downregulation of IgE antibody formation by allergen gene immunization.

AU Spiegelberg H.L.; Tighe H.; Roman M.; Beck L.; Raz E.
CS H.L. Spiegelberg, Department of Pediatrics 0833, University of California, San Diego School of Medicine, 9500 Gilman Drive, La Jolla, CA 92093-0833, United States. hansspieg@aol.com
SO Allergy and Clinical Immunology International, (1998) 10/2 (52-58).
Refs: 25
ISSN: 0838-1925 CODEN: ACIIFH
CY Switzerland
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB Classical immunotherapy carries the risk of anaphylaxis resulting from the injection of allergen and is therefore no longer used extensively. Recently, a novel form of immunization that does not involve injection of antigen, but rather plasmid DNA (pDNA) encoding the antigen, has been developed and could overcome the problem of anaphylaxis in immunotherapy, especially if it does not induce IgE. In this study we compared the **Th1/Th2** type immune response of mice to native protein antigen/allergen with that of immunization with pDNA encoding the same antigen. Protein immunization induced a Th2 response, as shown by IgG1 and IgE antibody formation and interleukin 4 (IL-4)- and IL-5-secreting T cells. In contrast, pDNA immunization induced a Th1 response with IgG2a antibody production and interferon γ (INF-γ)-secreting T cells. Furthermore, the pDNA-induced Th1 response dominated over the protein-elicited Th2 response. Mice primed with pDNA failed to produce IgE antibodies after a booster injection of allergen in alum. Boosting with pDNA of mice primed with antigen in alum resulted in a 75% decrease of the IgE titer, IgG2a antibody production, and INF-γ-secreting T cells. pDNA immunization also inhibited the eosinophilic infiltration of the lung induced by allergen inhalation in ovalbumin-sensitized mice. The mechanism of the pDNA elicited Th1 response was induction of IL-12 and INF-α/β secretion by accessory cells caused by noncoding immuno-stimulatory DNA sequences having the **CpG** motif in the backbone of the pDNA. The data indicate that gene vaccination induces a Th1 immune response to allergens that is capable of downregulating a preexisting Th2 response and IgE antibody formation. Thus, immunization with pDNA encoding for allergens may provide a novel type of immunotherapy for allergic diseases.

L8 ANSWER 157 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 80
AN 1998:33481 BIOSIS
DN PREV199800033481
TI **CpG** oligodeoxynucleotides act as adjuvants that switch on T helper 1 (Th1) immunity.
AU Chu, Rose S. [Reprint author]; Targoni, Oleg S.; Krieg, Arthur M.; Lehmann, Paul V.; Harding, Clifford V.
CS Inst. Pathol., Case Western Univ., Cleveland, OH 44106, USA
SO Journal of Experimental Medicine, (Nov. 17, 1997) Vol. 186, No. 10, pp. 1623-1631. print.
CODEN: JEMEAV. ISSN: 0022-1007.
DT Article
LA English
ED Entered STN: 14 Jan 1998
Last Updated on STN: 14 Jan 1998
AB Synthetic oligodeoxynucleotides (ODN) that contain unmethylated **CpG** motifs (**CpG** ODN) induce macrophages to secrete IL-12, which induces interferon (IFN)-gamma secretion by natural killer (NK) cells. Since these cytokines can induce T helper 1 (Th1) differentiation, we examined the effects of coadministered **CpG** ODN on the differentiation of Th responses to hen egg lysozyme (HEL). In both BALB/c (**Th2**-biased) and B10.D2 (**Th1**-biased) mice,

immunization with HEL in incomplete Freund's adjuvant (IFA) resulted in Th2-dominated immune responses characterized by HEL-specific secretion of IL-5 but not IFN-gamma. In contrast, immunization with IFA-HEL plus **CpG** ODN switched the immune response to a Th1-dominated cytokine pattern, with high levels of HEL-specific IFN-gamma secretion and decreased HEL-specific IL-5 production. IFA-HEL plus **CpG** ODN also induced anti-HEL IgG2a (a Th1-associated isotype), which was not induced by IFA-HEL alone. Control non-**CpG** ODN did not induce IFN-gamma or IgG2a, excepting lesser increases in B10.D2 (Th1-biased) mice. Thus, **CpG** ODN provide a signal to switch on Th1-dominated responses to coadministered antigen and are potential adjuvants for human vaccines to elicit protective Th1 immunity.

L8 ANSWER 158 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:241726 BIOSIS
DN PREV199799540929
TI Immune redirection by **CpG** oligonucleotides: Conversion of a **Th2** response to A **Th1** response in a murine model of asthma.
AU Kline, J. N.; Businga, T.; Weinstock, J. V.; Krieg, A. M.
CS Dep. Med., Univ. Iowa Coll. Med., Iowa City, IA, USA
SO Journal of Investigative Medicine, (1997) Vol. 45, No. 3, pp. 282A. Meeting Info.: Annual Meeting of the Association of American Physicians, the American Society for Clinical Investigation, and the American Federation for Medical Research: Biomedicine '97 Medical Research from Bench to Bedside. Washington, D.C., USA. April 25-27, 1997. ISSN: 1081-5589.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 2 Jun 1997
Last Updated on STN: 2 Jun 1997

L8 ANSWER 159 OF 159 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 81
AN 1994:532608 BIOSIS
DN PREV199497545608
TI Differentiation of the T helper phenotypes by analysis of the methylation state of the IFN-gamma gene.
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AB **Th1** and **Th2** CD4+ T cell clones have been defined by their ability to produce different lymphokines. However, the processes by which CD4+ T cells differentially regulate lymphokine gene expression have not been well defined. In this report, we demonstrate that the methylation status of a **CpG** dinucleotide contained within a TATA proximal regulatory element of the IFN-gamma promoter correlates with the transcription of the gene. In murine Th1 clones and two human CD4+ ThO clones, this site is either completely or partially hypomethylated, whereas in murine Th2 clones this site is gt 98% methylated. Treatment of murine Th2 clones with 5-azacytidine, an agent that inhibits methylation of the DNA, converts these cells to IFN-gamma producers. Additional targets for methylation outside the transcriptional control regions of the IFN-gamma genetic locus were found to be hypomethylated in **Th2**

cells but not in **Th1** cells. Electrophoretic mobility shift assays (EMSA) revealed at least five distinct protein-DNA complexes that are formed with an oligonucleotide containing the IFN-gamma promoter TATA proximal regulatory element, and in vitro methylation of this site results in a loss of these three complexes. Furthermore, a comparison of nuclear extracts prepared from **Th1** and **Th2** clones revealed that the EMSA patterns were qualitatively similar but differed quantitatively. In addition, transient transfection of a murine IFN-gamma promoter-chloramphenicol acetyl transferase (CAT) gene construct into both **Th1** and **Th2** clones produced CAT activity that was not inducible by anti-CD3, indicating that hypomethylation per se of the promoter alone is not sufficient for inducible gene expression.